ANALYSIS OF ANTIEPILEPTIC DRUG COMBINATIONS IN PATIENTS WITH EPILEPSY

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CERTIFICATE

This is to certify that the dissertation entitled **"ANALYSIS OF ANTIEPILEPTIC DRUG COMBINATIONS IN PATIENTS WITH EPILEPSY"** is a bonafide record of work done by **Dr. BALASUBRAMANIAM. S** in the Institute of Neurology, Rajiv Gandhi Government General Hospital & **MADRAS MEDICAL COLLEGE, CHENNAI** in partial fulfillment of the Tamilnadu Dr. MGR Medical University rules and regulations for the award of **D.M. (NEUROLOGY)** degree under my direct guidance and supervision during the academic year **2011-2014**.

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DECLARATION

I solemnly declare that this dissertation titled **"ANALYSIS OF ANTIEPILEPTIC DRUG COMBINATIONS IN PATIENTS WITH EPILEPSY"** is done by me in the Institute of Neurology, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai under the guidance and supervision of **Prof. K. BHANU, Dip.NB., D.M.,** Professor of Neurology, Institute of Neurology, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai. This dissertation is submitted to the Tamil Nadu Dr.MGR Medical University, Chennai in partial fulfillment of the university requirements for the award of the degree of D.M. Neurology.

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ABSTRACT

Purpose:

Epilepsy is a chronic neurological disorder that affects people of all age groups. Around 50 million people in the world have epilepsy, 5% to 10% of which live in India alone. 60% to 70% of people with epilepsy can be treated with simple monotherapy alone. The remaining patients require more than one drug for seizure control. But there is no consensus at present regarding the ideal Antiepileptic drug (AED) combinations. Our study examines epidemiological data, clinical characteristics of epilepsy, prescribing pattern of combination AEDs and their efficacy & adverse effect profile.

Methods:

200 patients with epilepsy attending the Epilepsy clinic of the Institute of Neurology, Madras medical college & Rajiv Gandhi Govt. General Hospital, Chennai, who were on AED polytherapy were included in the study after getting informed written consent. Complete history and physical examination were noted. Medication history was obtained from old records. Investigation reports were gone through.

Results:

Majority was middle aged, educated (65.5%) and employed (81.5%) males (61.5%). Idiopathic generalized seizures were more common (61%) than partial seizures. Structural lesions were present in 16.5% of patients and they had poor seizure control. More than half of the patients were treated with two drug AED combinations. 56.5% of patients were maintained on double drug combinations, 39.5% on three drug and 4% on four drug combinations. No combination had more than four drugs. Phenytoin was the commonly used antiepileptic drug in various combinations. Phenytoin and Carbamazepine were the commonly used double AED combination regimen. Phenytoin, Carbamazepine and Sodium valproate were the commonly used three drug AED combination regimen. Antiepileptic drugs of choice for generalized seizures and partial seizures were used in accordance with the recommended guidelines. Overall, 54% of patients had good seizure control with the combination AEDs. 50% of patients reported at least one minor adverse event, which did not require change of drugs. Adverse events were more common with three and four drug combinations than two drug combinations.

Conclusion:

Efficacy of conventional AED combinations in controlling seizures was comparable to newer antiepileptics. In cost constrained situations older AEDs are

as effective as newer and more costly AEDs. Though AEDs with similar mechanisms of action are generally not preferred due to the concern of additive side effects, in our study they were as effective as other combinations with different mechanisms of action. The adverse events were also comparable. Seizure control was better with two drug combinations than that of three and four drug combinations. Though monotherapy should be tried as for as possible, polytherapy remains the mainstay of treatment for large proportion of epileptic patients, particulalrly in cases of refractory epilepsy. Rational ploytherapy is a difficult to achieve goal with the knowledge available at present. It needs further research to find the ideal AED combinations. Treatment decision has to be made on an individual basis to make the polytherapy a successful one.

Introduction

Epilepsy is a chronic neurological disorder that affects people of all ages. Around 50 million people in the world have epilepsy.[1] 5% to 10% of which, i.e. 5-10 million people live with epilepsy in India alone.[2]

60% to 70% of people with epilepsy can be treated with simple monotherapy alone. The remaining patients require more than one drug for seizure control. But there is no consensus at present regarding the ideal Antiepileptic drug (AED) combinations.

Antiepileptic drugs act through many different mechanisms. By logical reasoning we can assume that combining drugs acting through same mechanism will lead to additive side effects. Hence it is reasonable to combine drugs with different mechanisms of action, particularly combining one drug having multiple mechanisms of action with another drug having single mechanism of action. This has been proven consistently in the synergistic combination of Valproic acid with lamotrigene.

More than 20 antiepileptic drugs are available in the market today. So selecting the combination will be a daunting task. However, when chosen carefully, combination AEDs may have synergistic efficacy with low adverse effects. Still further research is needed to identify the ideal combination.

Aim of the study

- To analyze the epidemiological data, clinical characteristics of epilepsy, prescribing pattern of combination antiepileptic drugs in a tertiary care hospital in Chennai
- To analyze the efficacy and adverse effect patterns of combination antiepileptic drugs.

Review of literature

Epilepsy is a chronic neurological disorder that affects people of all ages. According to WHO around 50 million people in the world have epilepsy.[1] Among them, developing countries contribute to nearly 80%. There may about 5-10 million people with epilepsy in India, which roughly corresponds to 0.5 – 1.0 % of the population.[2] Majority of people with epilepsy can be treated with simple drugs. Though Epilepsy responds to treatment in about 70%, three fourths of Epileptics in the developing countries do not get the treatment they need. Stigma and discrimination affects people with epilepsy and their families in many parts of the world, particularly in developing countries. The financial burden of treating epilepsy is enormous.

Definitions

Seizure

The International League Against Epilepsy (ILAE) defines epileptic seizure as ‘‘a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain’’[3]. The epileptic seizure may be characterized by motor, sensory, autonomic or psychic phenomena with or without loss of consciousness.[2]

Epilepsy

Epilepsyis a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure.

The revised ILAE Operational (Practical) Clinical Definition of Epilepsy [3]states thatEpilepsy is a disease of the brain defined by any of the following conditions:

1. At least two unprovoked seizures occurring more than 24 hours apart.

2. One unprovoked seizure and a probability of further seizures similar to the general recurrence risk after two unprovoked seizures (approximately 75% or more).

3. At least two seizures in a setting of reflex epilepsy.

Epilepsy is considered to be no longer present for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for at least 10 years off anti-seizure medicines, provided that there are no known risk factors associated with a high probability (>75%) of future seizures.

Drug Resistant Epilepsy

Drug resistant epilepsy may be defined as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.[4]

Seizure freedom

Freedom from all types of seizures for 12 months or three times the preinterventioninterseizure interval, whichever is longer.[4]

Classification of Seizures and Epilepsy:

Seizures and Epilepsy are classified by the International League Against Epilepsy by the two major schemes namely, International Classification of Epileptic Seizures (1981), and International Classification of Epilepsies and Epilepsy Syndromes (1989).

The concepts, terminology, and approaches for classifying seizures and epilepsy were revised by the ILAE Commission on Classification and Terminology (2010)[5]. However older classification systems are still continued to be used in wider clinical practice.

Classification of Seizures:

The 1981 classification dichotomized seizures as generalized and focal according to the extent of spread. Generalized seizures involve bilaterally distributed networks, whereas focal seizures spread within networks limited to one hemisphere. Table 1 shows classification scheme for Seizures.[6]

Table. 1

ILAE Classification of Epileptic Seizures
I. Partial (Focal, Local) Seizures **A.** Simple partial seizures (consciousness not impaired) **1.** With motor symptoms **2.** With somatosensory or special sensory symptoms **3.** With autonomic symptoms **4.** With psychic symptoms **B.** Complex partial seizures (with impairment of consciousness) **1.** With simple partial onset followed by impairment of consciousness **2.** With impairment of consciousness at onset **C.** Partial seizures evolving to secondarily generalized seizures **1.** Simple partial seizures evolving to generalized seizures **2.** Complex partial seizures evolving to generalized seizures **3.** Simple partial seizures evolving to complex partial seizures evolving to generalized seizures

II. Generalized Seizures (Convulsive or Nonconvulsive)

- **A.** Absence seizures
  - **1.** Typical absence seizures
  - **2.** Atypical absence seizures
- **B.** Myoclonic seizures
- **C.** Clonic seizures
- **D.** Tonic seizures
- **E.** Tonic-clonic seizures
- **F.** Atonic seizures

III. Unclassified Epileptic Seizures

Classification of Epilepsies and Epileptic Syndromes:

1989 ILAE Classification of Epilepsies and Epileptic syndromes has two important divisions. They first separated the generalized from localization related epilepsies. The other division separated epilepsies of known etiology (symptomatic) from unknown etiology. Epilepsies of unknown etiology were called idiopathic if there is no underlying cause could be found and considered to be genetic, or cryptogenic if occult underlying cause is suspected. Table 2 shows classification scheme for epilepsies and epileptic syndromes[7]

Table. 2

ILAE Classification of Epilepsies and Epileptic Syndromes
1. Localization-related (focal, local, partial) epilepsies and syndromes **1.1.** Idiopathic (with age-related onset) **1.2.** Symptomatic **1.3.** Cryptogenic **2. Generalized epilepsies and syndromes** **2.1.** Idiopathic (with age-related onset, listed in order of age appearance) **2.2.** Cryptogenic or symptomatic (in order of age) **2.3.** Symptomatic **2.3.1.** Nonspecific etiology **2.3.2.** Specific syndromes **3. Epilepsies and syndromes undetermined as to whether they are focal or generalized** **3.1.** With both generalized and focal seizures **3.2.** Without unequivocal generalized or focal features **4. Special syndromes** **4.1.** Situation-related seizures (Gelegenheitsanfälle) **4.1.1.** Febrile convulsions **4.1.2.** Isolated seizures or isolated status epilepticus **4.1.3.** Seizures occurring only when there is an acute metabolic or toxic event

Pathophysiology of Epilepsy:

Basic Mechanisms of Focal Seizure Initiation and Propagation[8]

During a seizure, hypersynchronus discharges may begin in a very discrete region of cortex and then spread to neighboring regions. Seizure initiation is characterized by two concurrent events:

1) **high-frequency bursts of action potentials** which lead to influx of extracellular Ca^{++}, which results in the opening of voltage-dependent Na^{+} channels. This leads to influx of Na^{+}, and generation of repetitive action potentials. Depending on the cell type, the subsequent hyperpolarizing afterpotential is mediated by either GABA receptors andCl^{-} influx, or by K^{+} efflux.

2) **hypersynchronization of a neuronal population:** When there is sufficient activation to recruit surrounding neurons, a partial seizure spreads within the brain by the process known as Seizure propagation. This leads to a loss of surround inhibition, which results in the spread of seizure activity into contiguous areas via local cortical connections, and to more distant areas via long association pathways such as the corpus callosum.

Epileptogenesis: The Transformation of a Normal Network Into a Hyperexcitable Network[8]

Patients with head injury usually do not present with seizures for months or years. This "silent period" after the initial injury shows that there is gradual transformation of the neural network to evolve into epileptogenic focus over time. Changes that occur during silent period could include delayed necrosis of inhibitory interneurons (or the excitatory interneurons driving them), or sprouting of axonal collaterals leading to reverberating, or self-reinforcing, circuits, Which results in long-lasting biochemical and/or structural changes in the CNS. However, the exact mechanisms underlying kindling, and its applicability to human epileptogenesis, remain unknown.

Pharmacotherapy:

The goal of pharmacological treatment of epilepsy is to obtain seizure control without adverse effects. Though idiopathic (primary) generalized epilepsies respond well to AEDs, 40% of patients with focal seizures related to structural lesions continue to have seizures even with optimal AED therapy. In them, atleast a balance between seizures and medication related side effects is expected.

Pharmacology of Antiepileptic drugs

Selection and optimization of AED therapy requires not only an understanding of drug mechanism of action and spectrum of clinical activity but also of pharmacokinetic variability and of particular drug related adverse events.

Nearly 14 antiepileptic drugs (AEDs) have been licensed for use in the past 20 years for common epilepsies and a range of more unusual syndromes. AEDs are classified into first, second and third generation drugs according to the year of entry into the market

Table. 3

First generation	**Second generation**	**Third generation**
Phenytoin	Gabapentin &Pregabalin	Lacosamide
Carbamazepine	Lamotrigine	Rufinamide
Phenobarbitone	Levetiracetam	Eslicarbazepine Acetate
Sodium Valproate	Topiramate	Retigabine
Benzodiazepine	Oxcarbazepine	Brivaracetam
Ethosuximide	Tiagabine	Perampanel
	Felbamate	Ganoxolone
	Vigabatrin	Carabersat

	Zonisamide Fosphenytoin	Carisbamate DP Valproic acid Fluorofelbamate Losigamone Remacemide Safinamide Seletracetam Stiripentol Talampanel

Mechanism of action of AEDs

AEDs act on ion channels located at the cell membrane to exert their antiseizure effects. Though these agents increase the threshold level for seizure, they have no effect on epileptogenesis.[9]

Table.4

Primary mechanism(s) of action of common AEDs[10]
Sodium channel blockers (a) Fast-inactivated state—phenytoin, carbamazepine, lamotrigine, oxcarbazepine,eslicarbazepine (b) Slow-inactivated state—lacosamide

Calcium channel blockers (a) Low voltage activated channel—ethosuximide (b) High voltage activated channel—gabapentin, pregabalin
GABA-ergic drugs (a) Prolongs chloride channel opening—barbiturates (b) Increased frequency of chloride channel opening—benzodiazepines (c) Inhibits GABA-transaminase—vigabatrin (d) Blocks synaptic GABA reuptake—tiagabine
Synaptic vesicle protein 2A modulation—levetiracetam
Carbonic anhydrase inhibition—acetazolamide
Multiple pharmacological targets—sodium valproate, felbamate, topiramate, zonisamide, rufinamide

In general, AEDs are better tolerated when started at low dose and gradually increased to the maximum dose.

The following table briefly mentions the starting and maintenance doses of commonly used AEDs

Table.5

Initial and maintenance daily doses, primary mode(s) of action and primary indications of commonly used AEDs[2,11]

AED	**Starting dose in average adult**	**Maintenance dose in average adult (mg/day)**	**Primary mode(s) of action**	**Indications (Seizure types/syndrome)**
Carbamazepine (CBZ)	100 mg BID	400 -1000	Blocks fast-inactivated state of Na^+ channel	Partial, GTCS
Clobazam (CLB)	10 mg OD (HS)	10-30	Activates GABAA receptor	Partial, GTCS
Lamotrigine (LTG)	25 mg OD (HS) Lower dose with VPA	100-300	Blocks fast-inactivated state of Na^+ channel/other mechanisms	Partial, GTCS
Levetiracetam (LEV)	250 mg BID	1000-3000	Modulates synaptic vesicle protein 2A	Partial, GTCS
Oxcarbazepine (OXC)	150 mg BID	600-1800	Blocks fast inactivated state of Na^+ channel	Partial, GTCS
Phenobarbitone (PB)	60-90 mg OD (HS)	60-180	Activates GABAA receptor	Partial, GTCS, myoclonic, tonic, clonic, SE
Phenytoin (PHT)	200-300 mg OD (HS)	200-400	Blocks fast-inactivated state of Na^+ channel	Partial, GTCS, SE

Topiramate (TPM)	25 mg OD	100 – 400	Various actions on multiple targets	Partial, GTCS, myoclonic, Lennox–Gastaut
Valproate (VPA)	200 mg BID	500-2000	Various actions on multiple Targets	Partial, GTCS
Zonisamide (ZNS)	50 mg OD (HS)	200-500	Various actions on multiple Targets	Partial, GTCS

Adverse effects of AEDs

Dose related adverse effects of AEDs can be managed by appropriate maintenance of serum drug concentrations. Also early identification of idiosyncratic AEs which poses significant health issues for PWE can be lifesaving. Drug interactions can be assessed by their pharmacokinetics and pharmacodynamic properties. Hepatic enzyme systems may facilitate AED interaction with other co administered medication through induction or inhibition of drug metabolism and result in AEs or seizures. Nearly 25% of patients become defaulters due to adverse effects with the initial AED chosen, and up to one-third are refractory despite repeated AEDs, potentially leading to recurrent adverse events and drug interactions.[12]

Table. 6

Antiepileptic Drugs and Their Common Acute, Chronic, and Idiosyncratic AdverseEffects[12]

Antiepileptic Drug	**Acute Adverse Effects**	**Chronic Affects**	**Idiosyncratic Affects**
Phenobarbital (PB)/ primidone (PRM)	Sedation, fatigue, ataxia, blurry vision	Hyperactive (children), learning, depression	Rash, connective-tissue disorders, hepatoxicity
Phenytoin (PHT)	Somnolence, dizziness, ataxia, blurry vision, N	Neuropathy, gum hyperplasia, hirsutism, low thyroid, osteoporosis	SJS, lupuslike reactions, pseudolymphoma, hepatitis, blood dyscrasias
Ethosuximide (ETH)	Somnolence, N/V/diarrhea, dizziness, anorexia, abdominal pain	Behavioral changes, irritability, nervousness, confusion, psychosis	SJS, lupuslike reaction, blood dyscrasias, hepatoxicity, generalized Sz increase
Carbamazepine (CBZ)	Somnolence, fatigue, rash, diplopia, dizziness,	Behavioral changes, low sodium,	SJS, hepatoxicity, aplastic anemia/low white

	ataxia, N/V	weight gain/edema	blood cell count
Valproic acid (VPA)	Abdominal pain, N/V/ diarrhea, hyperammonemia	Tremor, alopecia, amenorrhea, weight gain	Liver/pancreatic failure, low platelets, birth defects
Felbamate (FBM)	Headache, N/V, rash	Anorexia, weight loss, insomnia	SJS, aplastic anemia, hepatic failure
Gabapentin (GBP)/ pregabalin (PGB)	Somnolence, fatigue, ataxia, dizziness, blurry vision	Weight gain, pedal edema, behavior changes (children), creatine phosphokinase	None established
Lamotrigine (LTG)	Dizziness, diplopia, blurry vision, N/V, ataxia	Headache, insomnia, incoordination, tic	SJS, TEN, DRESS, myoclonic Sz increase
Topiramate (TPM)	Somnolence, dizziness, fatigue, anorexia, N	Mental slowing, speech and memory disturbance, paresthesias, weight loss, renal stones	Hepatic failure, oligohidrosis, glaucoma
Tiagabine	Headache, dizziness,	Abnormal	Nonconvulsive

(TGB)	fatigue, N/V, abdominal pain	thinking, tremor, nervousness	spike-wave stupor
Oxcarbazepine (OXC)	Somnolence, dizziness, fatigue, N/V	Hyponatremia (elderly), insomnia, headache	SJS, TEN
Levetiracetam (LEV)	Somnolence, dizziness, fatigue, N	Irritability, anger, anxiety, depression	None established
Zonisamide (ZNS)	Somnolence, ataxia, N/V, dizziness, fatigue	Lost appetite, speech, paresthesias, weight loss, renal stones, apathy	Rash, hypersensitivity reactions (sulfa)
Rufinamide (RUF)	Somnolence, N/V, headache, dizziness, fatigue	Incoordination, ataxia, shortened QT interval	Rash, DRESS
Lacosamide (LCS)	Somnolence, dizziness, N, fatigue, diplopia	Headache, tremor, ataxia, incoordination, depression	None established
Vigabatrin (GVG)	Somnolence, dizziness, fatigue	blurred vision, arthralgia	Permanent visual field

		Weight gain, edema, neuropathy, depression	loss, psychosis

N = nausea; V = vomiting; Sz = seizure; DRESS = drug reactions with eosinophilia and systemic symptoms; TEN = toxic epidermal necrolysis; SJS = Steven-Johnson syndrome.

General Approach to Treatment

Regarding the initiation of pharmacologic therapy the recent 2012 NICE (National Institute of Health and Care Excellence) guidelines, which was updated in December 2013 says that[13]

- AED therapy should be started only after the diagnosis of epilepsy is confirmed.
- Treatment with AED is generally recommended after a second seizure. However in conditions where the individual has a neurological deficit, the EEG shows unequivocal activity and a structural abnormality is seen in the brain, AEDs may be started after the first seizure.
- The decision to initiate AED therapy should be taken after a full discussion with the patient, their relatives about the risks and benefits.
- Individuals should be treated with a single antiepileptic drug (Monotherapy) wherever possible. If the initial treatment is unsuccessful, then monotherapy

using a second drug can be tried. If an AED has failed due to adverse effects or continued seizures, then a second drug is started (which is an alternative first line or second line drug) and built up to an adequate or maximum tolerated dose; then the first drug is slowly tapered.

- It is recommended that only when attempts at monotherapy with AEDs have failed, combination AED therapy (adjunctive or add on therapy) should be considered.
- Combination of drugs with different mechanisms of action is considered advantageous.

When to stop AEDs?

There are no well accepted guidelines regarding the time at which AEDs can be stopped. However with available studies it has been possible to withdraw the AEDs in many patients who have been seizure free for 2 to 5 years.[14] The benefits associated with discontinuation of AEDs must be weighed against the possibility that a seizure may recur again. In 26 to 63% of adults, relapse occurs within one to two years after AED withdrawal.[9] Predictors of relapse include an abnormal EEG prior to or during medication withdrawal, abnormal neurological exam, mental retardation, and frequent seizures prior to withdrawal. Successful AED withdrawal in adults is more likely after a longer seizure free period. However, there are a few

epilepsy syndromes for which the chance of recurrence is so high that AED discontinuation is not suggested. These include juvenile myoclonic epilepsy and reading epilepsy.[15] Medication withdrawal should not proceed faster than a 20% dose reduction every five half-lives unless there is a definite need for more rapid discontinuation.

Selection of AEDs

For initial monotherapy of partial seizures, high-level of evidence exists for the efficacy of carbamazepine, oxcarbazepine, and topiramate and for initial monotherapy of generalized seizures, high-level evidence is available for valproate, lamotrigine, topiramate, and oxcarbazepine.

For initial monotherapy of absence seizures, high level evidence exists for valproate, lamotrigine, and ethosaximide.[16] All second generation AEDs have efficacy as adjunctive therapy for partial seizures.

AEDs should be selected on the basis of comorbid conditions, including depression, migraine, chronic pain, obesity, and nephrolithiasis, or patient characteristics, especially for women of childbearing potential and older adults, as

AEDs are often useful for comorbid conditions or have properties that should be avoided in some groups.

Table.7

AEDs : Level of evidence for each seizure type and epilepsy syndrome[17]	
Seizure type or epilepsy syndrome	**Level of efficacy and effectiveness evidence (in alphabetical order)**
Adults with partial-onset seizures	Level A: CBZ, LEV, PHT, ZNS Level B: VPA Level C: GBP, LTG, OXC, PB, TPM, VGB Level D: CZP, PRM
Children with partial-onset seizures	Level A: OXC Level B: None Level C: CBZ, PB, PHT, TPM, VPA, VGB Level D: CLB, CZP, LTG, ZNS
Elderly adults with partial-onset seizures	Level A: GBP, LTG Level B: None Level C: CBZ Level D: TPM, VPA
Adults with generalized onset tonic–clonic seizures	Level A: None Level B: None Level C: CBZ, LTG, OXC, PB, PHT, TPM, VPA Level D: GBP, LEV, VGB

Children with generalized-onset tonic–clonic seizures	Level A: None Level B: None Level C: CBZ, PB, PHT, TPM, VPA Level D: OXC
Children with absence seizures	Level A: ESM, VPA Level B: None Level C: LTG Level D: None
Benign epilepsy with centrotemporal spikes (BECTS)	Level A: None Level B: None Level C: CBZ, VPA Level D: GBP, LEV, OXC, STM
Juvenile myoclonic epilepsy (JME)	Level A: None Level B: None Level C: None Level D: TPM, VPA

Monotherapy or Polytherapy?

Until the early 80's, polytherapy was widely practiced as first line treatment for refractory epilepsy with the hope that there will be less severe drug toxicity when two drugs with lower doses are combined.[18] Subsequent trials by Shorvon& Reynolds (1979) and Schmidt (1983) lead to a change from monotherapy to polytherapy.[19]

Up to 2/3 of patients respond initially to single AED; approximately 47% respond to the initial AED, if they don't respond, substitution of a second AED may benefit another 13% of patients.[20] If those two drugs do not control seizure, there is only small chance of success with further monotherapy trials. The remaining patients require more than one AED for seizure control.[21]

With the addition of more than 14 new drugs over the past two decades, the combinations and permutations became numerous (200 double drug combinations or more than 1000 triple drug combinations).

The clinical effects of two drugs, when a second drug being added to a patient on monotherapy could result in three outcomes:

(1)Additive

(2)Supra-additive or

(3)Infra-additive or antagonistic

For better clinical outcome, regarding clinical effectiveness, synergy (at least additivity) is desirable; for adverse effects, antagonism is preferable.The following table lists some of the favourable and unfavourable AED combinations

Table.8[18]

Favourable AED combinations	
CBZ	GBP, LEV, OXC, TPM, VPA
CZP	OXC
ESX	VPA
FBM	LEV, LTG, TPM
GBP	LEV, LTG, OXC, PB, PHT, TGB, TPM, VIG, VPA
LEV	CBZ, FBM, OXC, PB, TPM
LTG	FBM, GBP, TPM, VPA
OXC	CBZ, CZP, GBP, LEV, TPM
PB	GBP, LEV, PHT
PHT	GBP, PB, VPA
TGB	GBP, VIG, VPA
TPM	CBZ, FBM, GBP, LEV, LTG, OXC, VPA
VIG	GBP, TGB
VPA	CBZ, ESX, GBP, LTG, PHT, TGB, TPM
Unfavourable AED combinations	
CBZ	LTG
CZP	FBM
FBM	CBZ, OXC, TGB, VPA
LTG	CBZ, OXC
OXC	FBM, LTG, PHT
PHT	OXC
TGB	FBM
VPA	FBM

Although it's not possible always to have combination with synergistic clinical effect and antagonistic adverse effects all the times, it might be acceptable to have a drug combination with intermediate effects, i.e., additive with regard to their clinical effect but antagonistic with regard to their side effects or two drugs that are synergistic clinically but only additive adverse effects.

Clinical considerations inPolytherapy

The choice of optimal polytherapy is difficult for many reasons. Foremost among them is, the availability of very limited data regarding the favourable or unfavourablecombinaitons. Also, there is only very little systematic evidence available as any one combination is more or less effective than others.[18]

Combination therapy with different mechanisms of action has been generally preferred since theoretically small effects on multiple drug targets may be more effective than drugs acting on single mechanism of action. Studies have shown that the combination of sodium channel blockers, Phenytoin and Carbamazepine, is less effective than with either in combination with Phenobarbitone.[22] Drugs with similar mechanism action may have similar side effect profiles, resulting in additive side effects in such combinations. Some studies have shown that even drugs with similar mechanisms of action such as Phenytoin and Carbamazepine

produce different adverse effect profiles.[23] Furthermore, combination of two drugs with completely different mechanisms of action may have similar side effects by acting upon unidentified targets which not related to their antiepileptic mechanisms.[24]

In summary, there is insufficient evidence at present to provide meaningful guidelines to determine whether similar or different mechanism of action should be targeted for rational combination of AEDs. This appears true for both efficacy and adverse effect profile. Nonetheless, two AEDs with virtually identical mechanisms of actions should be avoided to minimize adverse effects.

Guidance for combining Antiepileptic drugs

While rational polytherapy remains an elusive goal, guidelines for the approach to monotherapy should also apply for combinations of AEDs, although there would potentially be exaggerated clinical pitfalls:

Table 9

Guidance for combining antiepileptic drugs[10]
➢ Establish optimal dose of baseline agent ➢ Add drug with multiple mechanisms ➢ Avoid combining similar modes of action ➢ Titrate new agent slowly and carefully

- Be prepared to reduce dose of original drug
- Replace less effective drug if response still poor
- Try range of different duotherapies
- Add third drug if still sub-optimal control
- Devise palliative strategy for refractory epilepsy

Pharmacokinetic interactions of the AEDs used should be carefully evaluated, especially for drugs affecting hepatic drug metabolizing enzymes[25] and for the elderly who are more likely to be on multiple medications due to the associated comorbid illnesses.

Presence of concurrent medical or psychiatric conditions such as depression or migraine should be considered carefully. Polytherapy should be better avoided during pregnancy, if possible, especially if it includes Sodium valproate.[26]

Finally, it has to be kept in mind that the patient may be less compliant with a more complex regimen. Expenditure for drugs will invariably be greater. Extreme caution should be taken to minimize medication errors.

Material and Methods

Place of study

The study was conducted at the Epilepsy Clinic, Institute of Neurology, Madras Medical College & Rajiv Gandhi Government General Hospital, a teaching institute and 3000 bedded tertiary care hospital situated at Chennai, catering to the needs of Northern parts of the state of Tamilnadu and adjoining parts of Andhra Pradesh. The patient population includes fair representation from urban and rural areas. It includes people from varied socioeconomic strata particularly belonging to lower and middle socioeconomic groups. The study population was those patients who are attending the Epilepsy Clinic for Antiepileptic Drugs. Institutional ethics committee approval was obtained for the study.

Study design and duration

The study was a cross sectional descriptive study, which was conducted between August to December 2013. Everyday approximately 200 to 250 patients attend our Epilepsy clinic for Antiepileptic drugs. 200 consecutive patients who met our inclusion and exclusion criteria were selected for the study after obtaining informed consent.

Inclusion Criteria

1. Epileptic patients who are on combination Antiepileptic drugs for more than a year

2. Those patients who consented to participate in this study after detailed explanation in their mother tongue, mostly Tamil.

3. Those patients with proper treatment records

Exclusion Criteria

1. Epileptic patients who are on monotherapy

2. Patients not consented for participating in the study

3. Patients without proper treatment records

4. Those with poor drug compliance according to the attenders and patients themselves

5. Patients with major psychiatric illness like schizophrenia and major depression

Methods of data collection

The eligible patients were identified from patient files and they were enrolled in our study after written informed consent. The study objective and process were explained to the patients and attenders in their mother tongue for obtaining the consent. Patients who consented were interviewed for obtaining relevant data.

The data were collected in the proforma specifically designed for the study. The data included,

1. Demographic data: Patient name, age, sex, address, occupation and average monthly income were obtained

2. Disease data: Seizure types, frequency, age of onset and duration, time since last seizure, family history of seizure and other comorbid illness were obtained. Seizure freedom is defined Freedom from all types of seizures for 12 months or three times the preintervention interseizure interval, whichever is longer.[4]

3. Treatment data: Treatment details including names of the drugs used, starting and maximum dosages, duration of treatment, details regarding compliance, adverse effects an intake of other medications were recorded

4. Investigation data: Details of investigations done and their findings were recorded, which included EEG, CT Brain, MRI Brain and CSF analysis, complete hemogram, blood biochemistry and other relevant investigations.

Methods of data analysis

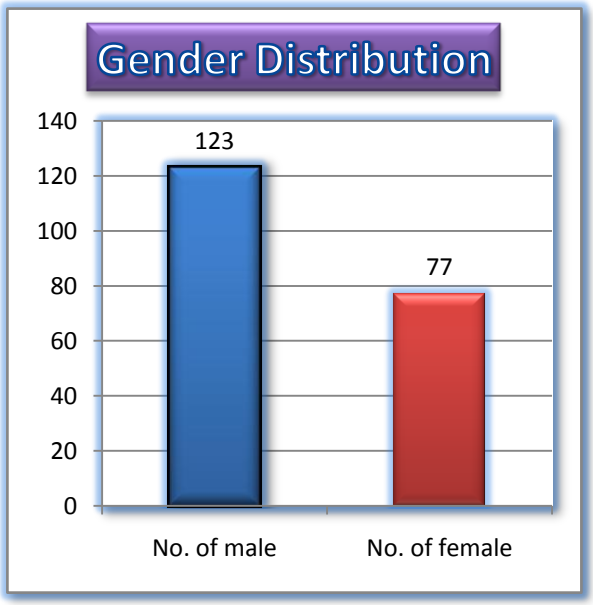
All the collected data were entered into Microsoft Windows 2010 excel spreadsheet and analyzed with the help of Microsoft excel and SPSS software.

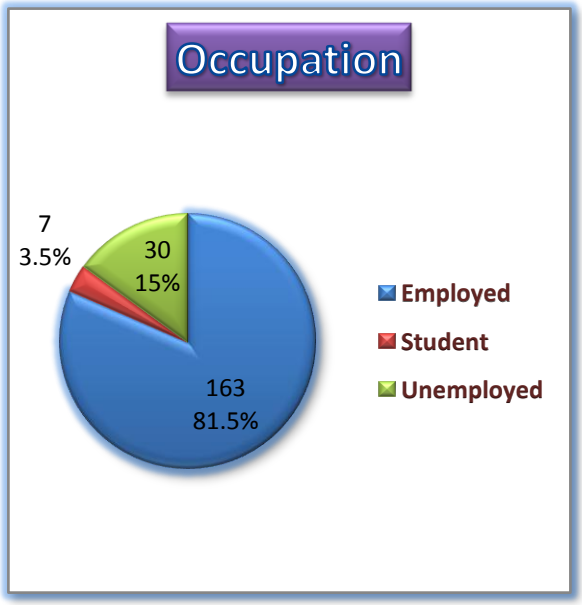
Results& Analysis

200 patients who were found to be eligible and consented for the study were recruited from August to December 2013 and analyzed.

Patient characteristics and Demographic profile

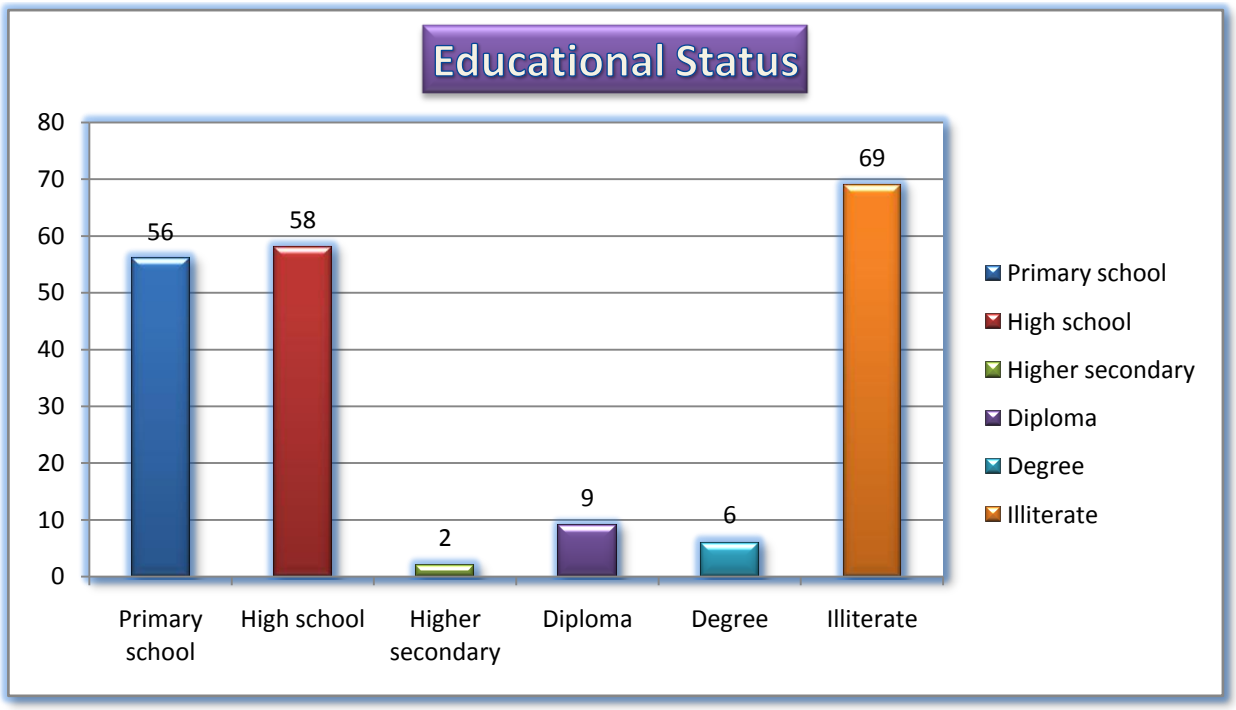
Out of 200 patients 123 (61.5%) were males and remaining 77 (38.5%) were females. Mean age of the patients on treatment with Antiepileptic drugs was 44.56±12.05 years with age ranging from 12 years to 71 years. Mean age of males was 43.64±12.41 years with age ranging from 12 years to 71 years; mean age of females was 46.01±11.39 years with age ranging from 18 years to 70 years





Of the 200 patients, 163 (81.5%) were employed, seven (3.5%) were students and the remaining 30 (15%) were unemployed.

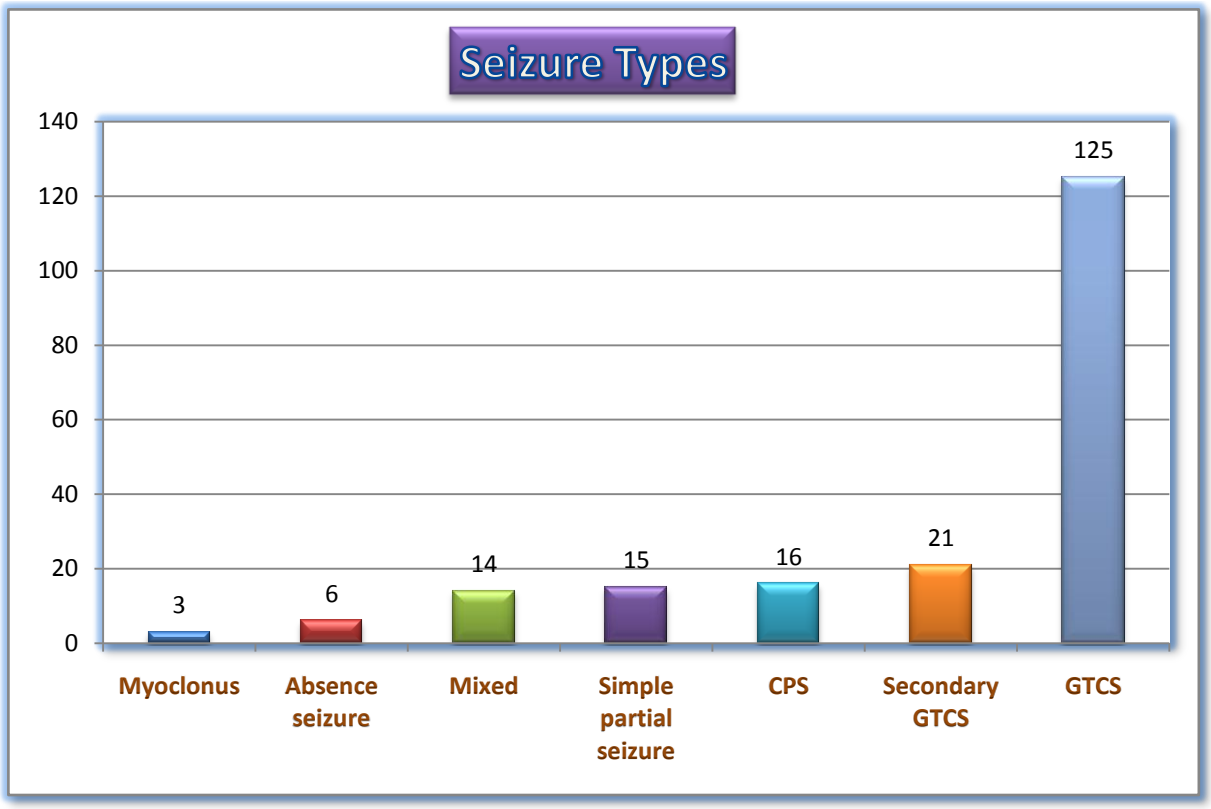
Majority of the patients were illiterate. Only 15 (7.5%) patients went to college and 69 (34.5%) were illiterate.



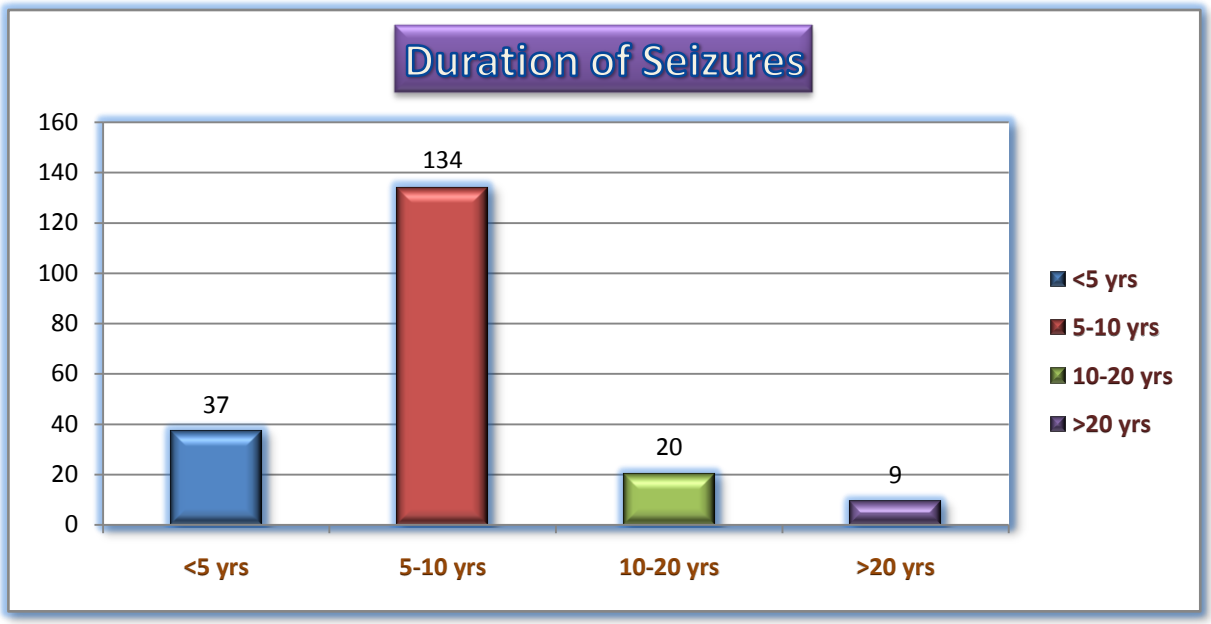
Clinical characteristics of patients with epilepsy

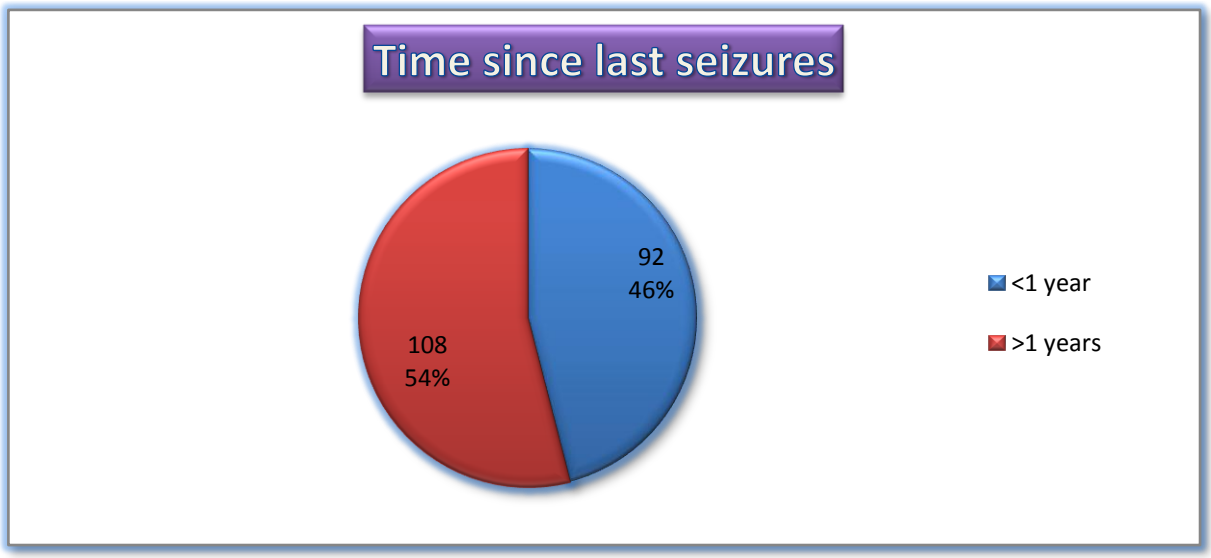
Out of 200 patients, 134 (67%) had generalized seizures, 52 (26%) had partial seizures with the remaining 14 (7%) had mixed seizure types. Generalized tonic clonic seizure was the most common type of seizure which was present in 125

(62.5%) patients, followed by absence seizures in 6 (3%), myoclonus in 3 (1.5%), simple partial seizures in 15 (7.5%), partial seizure with secondarily generalized seizures in 21 (10.5%), Complex partial seizure in 16 (8%) and mixed seizure types in 14 (7%) patients.



Mean duration of the seizures was 8.07±5.48 years, ranging from 2 years to 40 years. 37 (18.5%) patients had duration of seizures < 5 years, 134 (67%) patients had seizures between 5 and 10 years, 20 (10%) had seizures between 10 and 20 years, 9 (4.5%) had seizures > 20 years. 108 (54%) patients were free of seizures which is defined as free from seizures for more than a year as per ILAE definition.[4]





33 (16.5%) patients had structural lesions in neuroimaging. Two patients had postencephaliticsequalae out of which one of them was on ventriculoperitoneal (VP) shunt, 11 patients had gliosis, nine patients had cerebral atrophy, four patients had calcified granuloma, three patients had CNS tumors (two gliomas and one meningioma), two patients had Mesial temporal lobe sclerosis (MTLS).

Out of 33 patients with structural lesions, 12 (6%) patients had GTCS, 3 (1.5%) had simple partial seizures, 17 (8.5%) had partial seizures with secondary generalization and 1 (0.5%) had mixed seizure type. None of the patients with complex partial seizures, myoclonus or absence seizures had structural lesions. Only 5 patients (4 GTCS, 1 Partial seizure with secondary generalization) with structural lesions had seizure freedom. Remaining 28 patients were not under seizure control. Table shows the relationship between the presence of structural lesions and seizure freedom in various types of seizures.

Electroencephalogram (EEG) abnormalities found in 72 (36%) patients. CSF analysis was done in 13 (6.5%) patients, out of which 8 had abnormal findings.

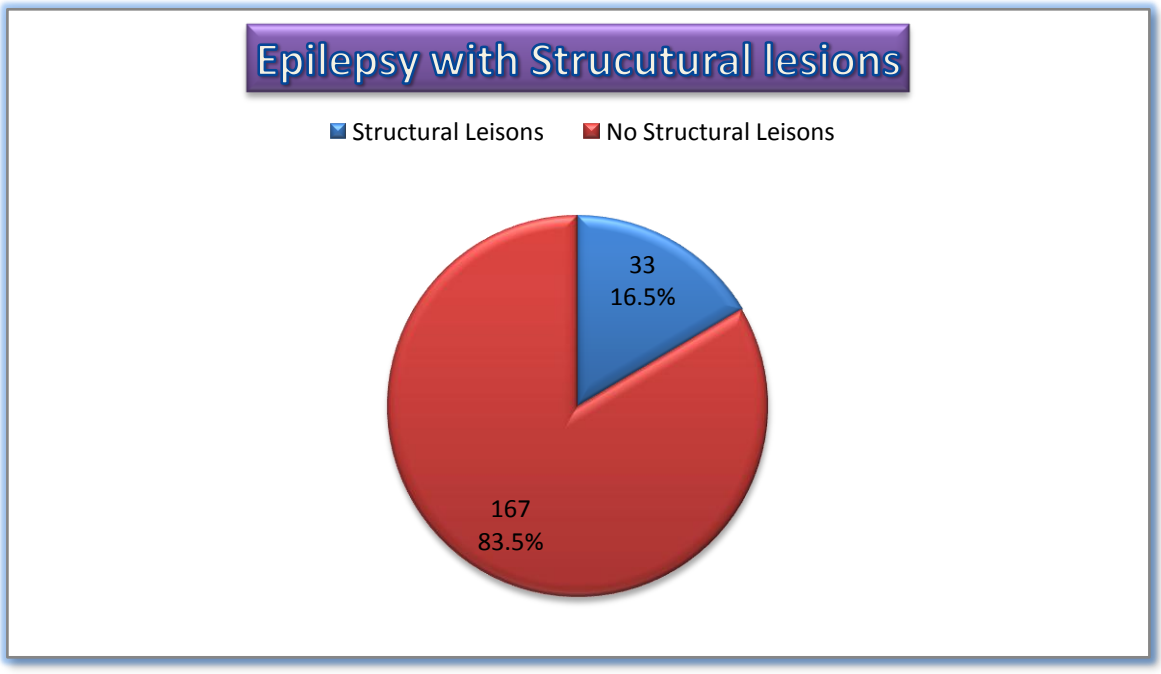
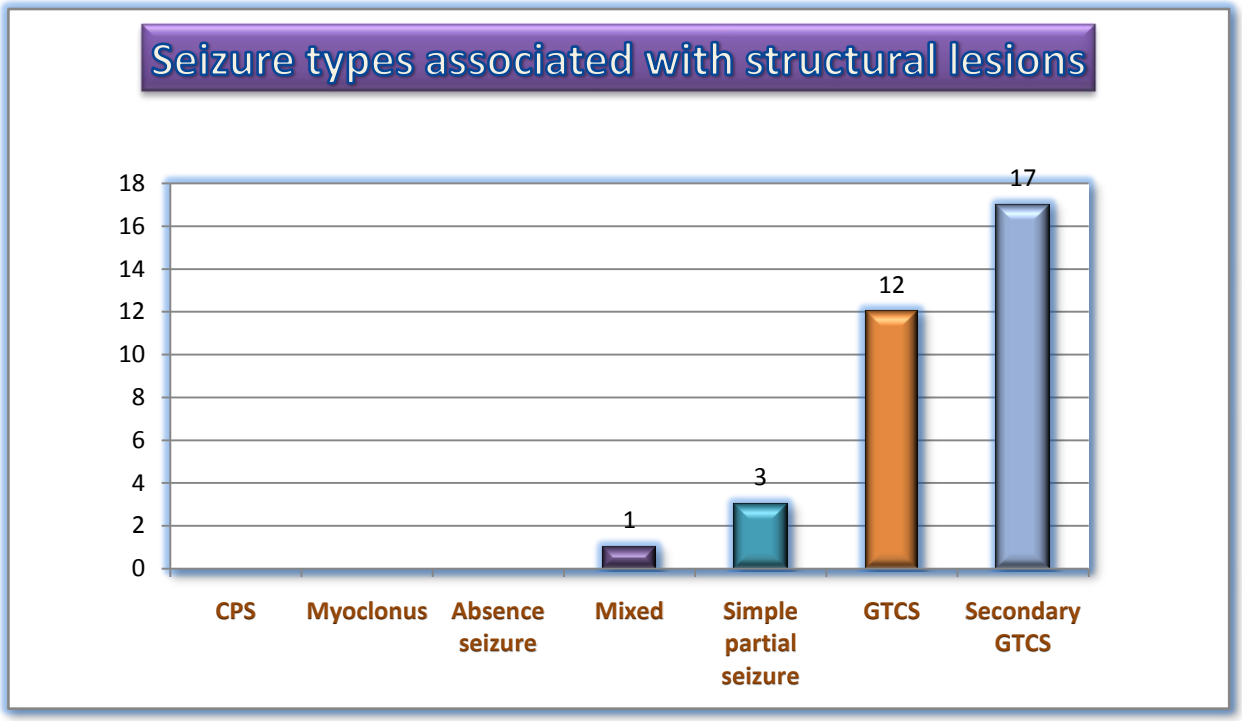


Table.10

Structural Lesion	**Seizure type**	**Seizure Freedom**		**Total**
		Yes	No	
No	Absence seizure	3	3	6
	CPS	10	6	16
	GTCS	67	46	113
	Mixed (GTCS/AB)	2	2	4
	Mixed (GTCS/MYO)	7	2	9
	Myoclonus	3	0	3
	Partial seizure with Secondary Generalization	4	0	4
	Simple partial seizure	7	5	12
	Total	103	64	167
Yes	GTCS	4	8	12
	Mixed (GTCS/MYO)	0	1	1
	Partial seizure with Secondary Generalization	1	16	17
	Simple partial seizure	0	3	3
	Total	5	28	33
Total	Absence seizure	3	3	6
	CPS	10	6	16
	GTCS	71	54	125
	Mixed (GTCS/AB)	2	2	4
	Mixed (GTCS/MYO)	7	3	10
	Myoclonus	3	0	3
	Partial seizure with Secondary Generalization	5	16	21
	Simple partial seizure	7	8	15
	Total	108	92	200



40 (20%) patients had comorbid illness, with Diabetes mellitus (DM) in 16 (8%) patients,Hypertension in 15 (7.5%), Chronic obstructive pulmonary disease (COPD) in 5 (2.5%)and Bronchial asthma in 4 (2%), who were on medications for the conditions. 69(34.5%) patients used to consume alcohol regularly.

Pharmacotherapy characteristics

Phenytoin was the most commonly used AED, which was used in 180 (90%) patients, followed by Carbamazepine in 157 (78.5%) patients and Sodium valproate in 144 (77%) patients, Phenobarbitone in 7 (3.5%) patients, Levetiracetam in 5 (2.5%) patients and Clonazepam in 2 (1%) patients.

The mean dosage of Phenytoin was 282 mg/day with dosage ranging from 100 mg/day to 400 mg/day. Phenytoin dose was suboptimal at 100 mg/day in 12 patients, of which 10 patients were not under seizure control.

The mean dosage of Carbamazepine was 1052 mg/day with dosage ranging from 200 mg/day to 1400 mg/day. Carbamazepine dose was suboptimal in 9 patients. 4 patients were on 200 mg/day and 5 patients were on 300 mg/day. Seizures were not controlled in 6 patients.

The mean dosage of Sodium valproate was 1017 mg/day with dosage ranging from 400 mg/day to 1400 mg/day. Sodium valproate dose was suboptimal at 400 mg/day in 17 patients. Seizures were not controlled in 7 patients.

The mean dosage of Phenobarbitone was 80 mg/day with dosage ranging from 60 mg/day to 120 mg/day. The mean dosage of Levetiracetam was 1400 mg/day with dosage ranging from 1000 mg/day to 1500 mg/day. The mean dosage of Clonazepam was 0.5 mg/day.

Antiepileptic drug prescribing pattern in individual seizure types

The prescribing pattern of AEDs for the underlying seizure type was appropriate in most of the situations except in few cases. Carbamazepine was prescribed as first line drug in one patient with absence seizure and one patient with mixed seizure having myoclonic seizure. Phenytoin was prescribed as a first line drug in a patient myoclonus, another patient with mixed seizure type having absence seizure and in three patients with mixed seizure type having myoclonic seizures.

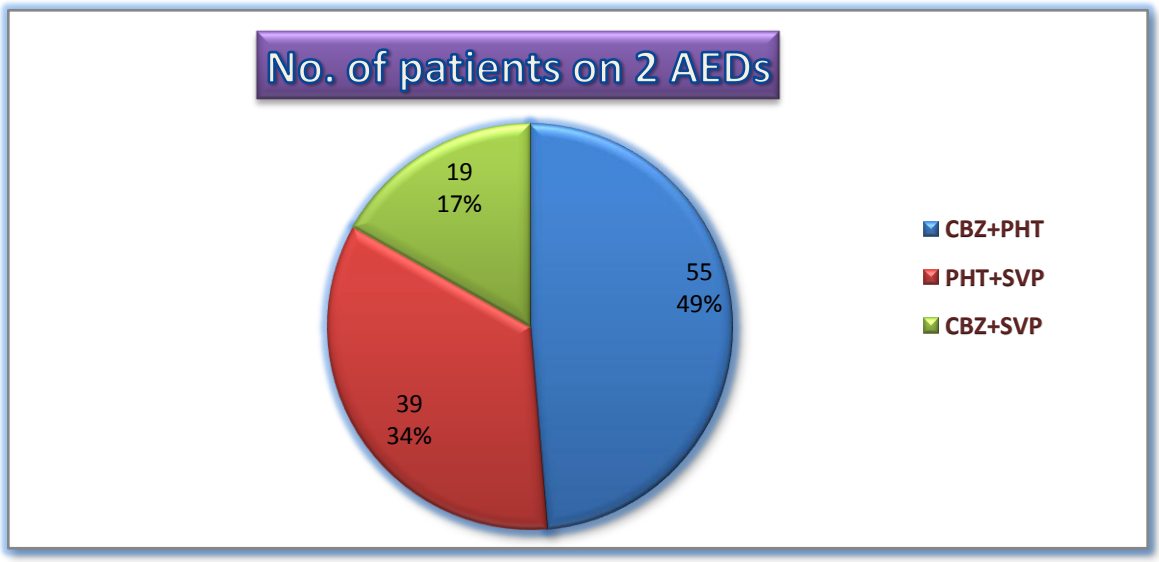
Table.11

Seizure types	Commonest drugs prescribed	Second commonest drug prescribed	Other drugs prescribed
GTCS	PHT	CBZ	SVP
Absence seizures	SVP	PHT	CBZ
Simple partial seizure	CBZ	PHT	SVP
Partial seizure with sec. generalization	CBZ	PHT	SVP
Complex partial seizure	CBZ	SVP	PHT
Myoclonic epilepsy	SVP	PHT	CBZ

Pattern of Antiepileptic drug combinations

113 (56.5%) Patients were on double AED therapy. 79 (39.5%) patients were on three drug AED therapy and 8 (4%) patients were on four drug AED therapy.

Double Antiepileptic drug combinations



Out of the 113 patients on two drug AED therapy, 55 patients were on Phenytoin and Carbamazepine duotherapy, which was the most common combination duotherapy. The other duotherapy combinations are Phenytoin and Sodium valproate (39 patients) and Carbamazepine and Sodium valproate (19 patients). 34 patients on duotherapy containing Phenytoin and Carbamazepine had seizure freedom for more than a year. 25 patients on duotherapy containing Phenytoin and Sodium valproate had seizure freedom for more than a year. 11 patients on duotherapy containing Sodium valproate and Carbamazepine had seizure freedom

for more than a year. Three out of 55 patients on Phenytoin and Carbamazepine combination and two out of 19 patients on Carbamazepine and Sodium valproate combination had structural lesions in neuroimaging.

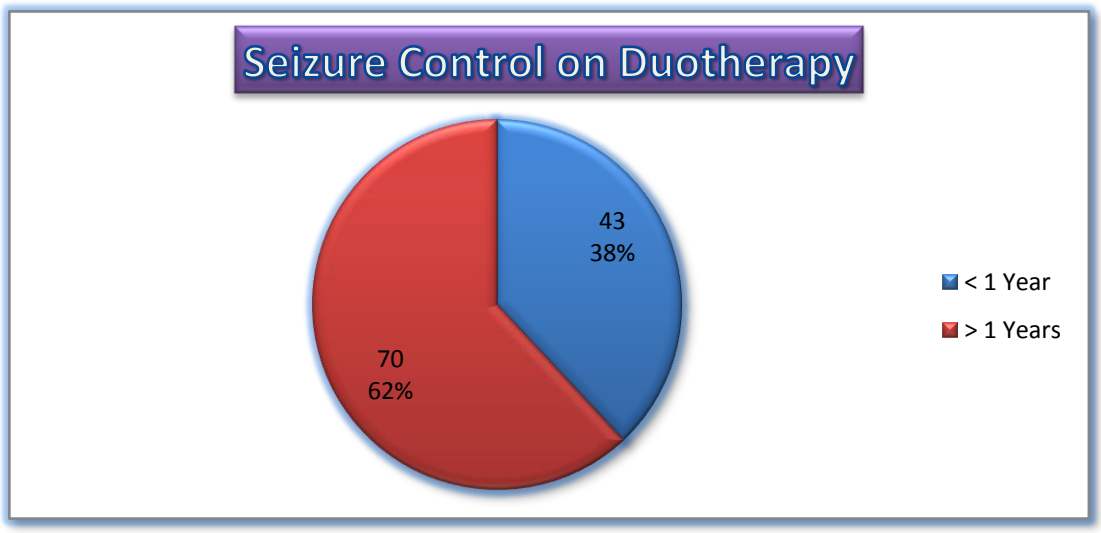


Table.12 Comparision of Seizure freedom in two drug AED Combination

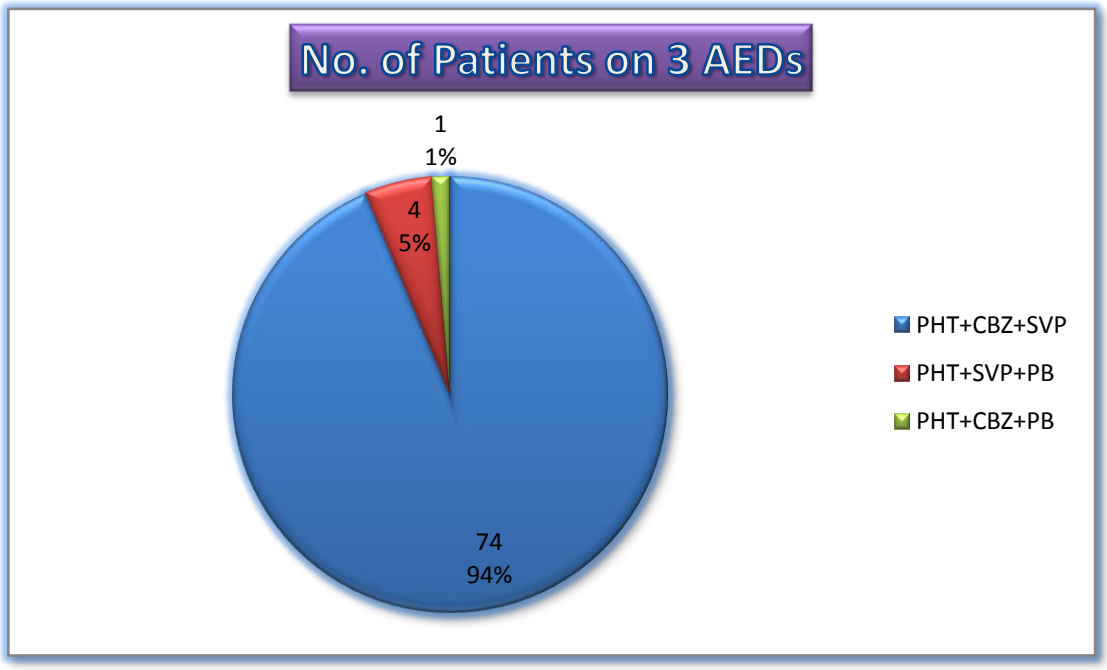
Combination	**Seizure freedom**		**Total**
	Yes	**No**	
PHT+SVP	25	14	39
	GTCS 20 Absence 1 Myoclonus 1 Simple partial 0 CPS 0 Partial with sec gen 0 Mixed 3	GTCS 13 Absence 1 Myoclonus 0 Simple partial 0 CPS 0 Partial with sec gen 0 Mixed 0	

PHT+CBZ	34	21	55
	GTCS 26 Absence 0 Myoclonus 0 Simple partial 3 CPS 3 Partial with sec gen 2 Mixed 0	GTCS 15 Absence 0 Myoclonus 0 Simple partial 3 CPS 1 Partial with sec gen 2 Mixed 0	
CBZ+SVP	11	8	19
	GTCS 1 Absence 0 Myoclonus 0 Simple partial 3 CPS 3 Partial with sec gen 1 Mixed 3	GTCS 0 Absence 1 Myoclonus 0 Simple partial 0 CPS 5 Partial with sec gen 2 Mixed 0	
Total	70	43	113

Chi Square test

	Value	**df**	**Asymp. Sig (2 sided)**
Pearson Chi-Square	0.210	2	0.900

Triple Antiepileptic drug combinations



79 patients were on AED combinations containing three drugs. 74 patients were on Phenytoin, Carbamazepine and Sodium valproate combination, which was the most common triple AED combination. 4 patients were on Phenytoin, Sodium valproate and Phenobarbitone combination. One patient was on Phenytoin, Carbamazepine and Phenobarbitone combination. Out of 74 patients on Phenytoin, Carbamazepine and Sodium valproate combination 25 patients had structural lesions in neuroimaging. One patient had structural lesion in the Phenytoin, Sodium valproate and Phenobarbitone combination. 34 patients had adequate control with seizure freedom for more than a year. 30 out of 74 patients on Phenytoin, Carbamazepine and Sodium valproate combination, 3 out of 4 patients on Phenytoin, Sodium valproate and Phenobarbitone combination and the single

patient on Carbamazepine, Sodium valproate and Phenobarbitone combination had seizure freedom for more than a year.

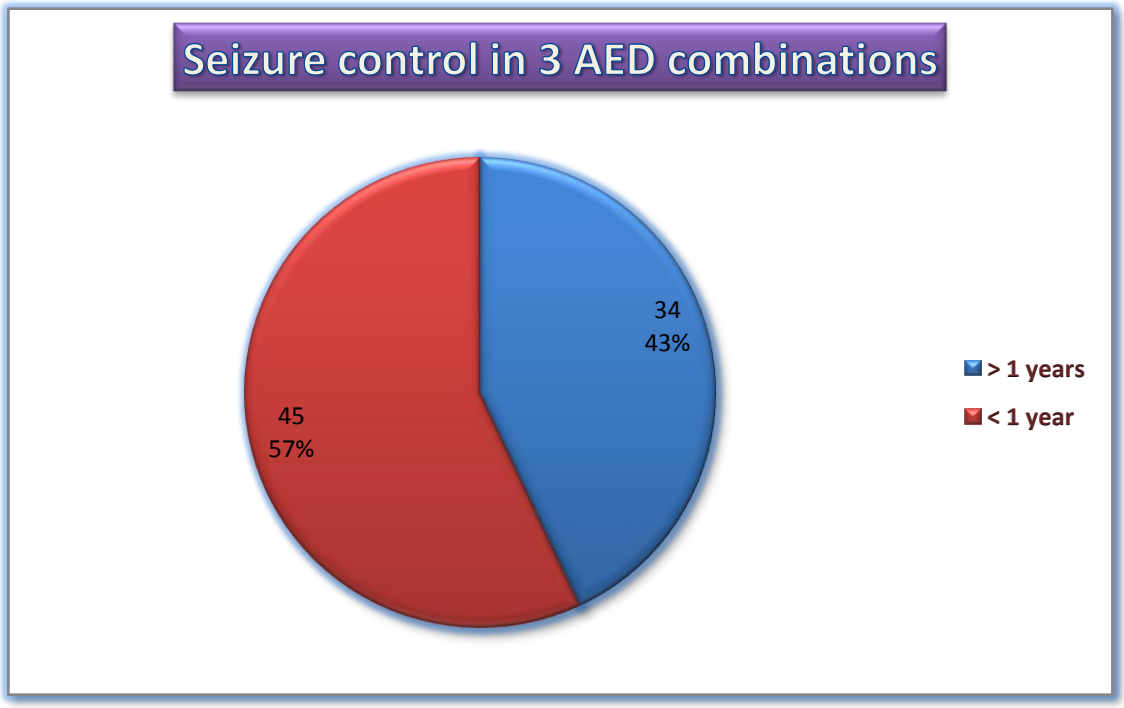


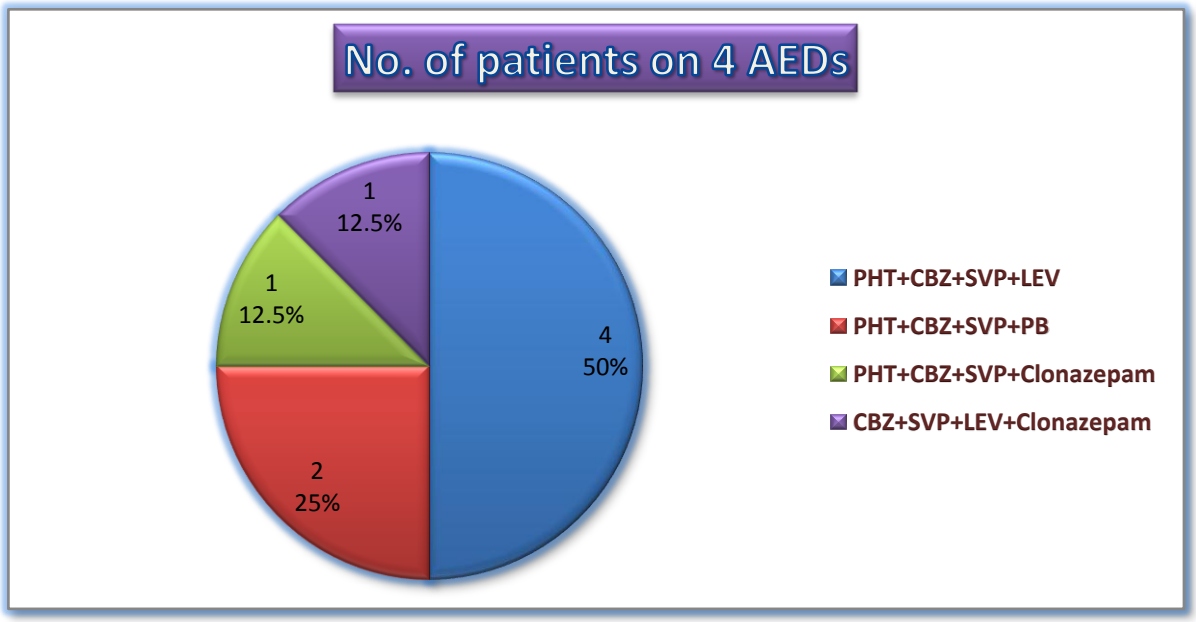
Table.13 Comparision of Seizure freedom in 3 drug AED Combinations

Combination	**Seizure freedom**		**Total**
	YES	**NO**	
PHT+CBZ+SVP	30	44	74
	GTCS 17 Absence 2 Myoclonus 2 Simple partial 1 CPS 4 Partial with sec gen 2 Mixed 2	GTCS 21 Absence 1 Myoclonus 0 Simple partial 5 CPS 0 Partial with sec gen 12 Mixed 5	
PHT+CBZ+PB	1 (GTCS 1)	0	1
PHT+SVP+PB	3 (GTCS 3)	1 (GTCS 1)	4
Total	34	45	79

Chi-Square tests

	Value	df	Asymp. Sig. (2 sided)
Pearson Chi-Square	3.179	2	0.204

Four Antiepileptic drug combinations



Eight patients were on four drug AED combinations. The most common combination being Phenytoin, Carbamazepine, Sodium valproate and Levetiracetam taken by four patients. Two patients were on Phenytoin, Carbamazepine, Sodium valproate and Phenobarbitone combination. One each in Phenytoin, Carbamazepine, Sodium valproate, Clonazepam and Carbamazepine, Sodium valproate, Levetiracetam, Clonazepam combinations respectively. Two patients had structural lesions.

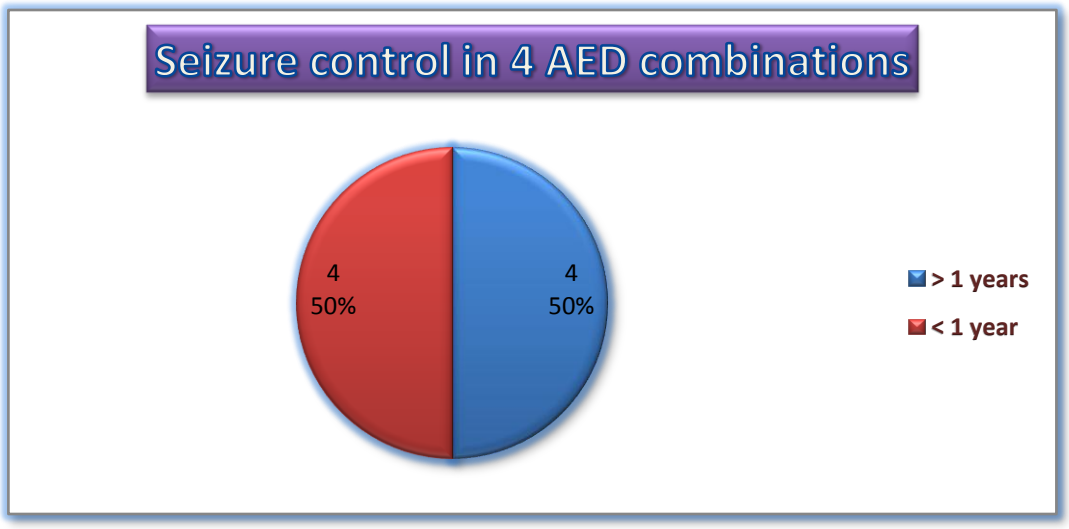


Table.14 Comparison of Seizure freedom in 4 drug AED Combination

Combination	**Seizure freedom**		**Total**
	Yes	**No**	
PHT+CBZ+SVP+CLO	0	1 (GTCS 1)	1
PHT+CBZ+SVP+PB	1 (GTCS 1)	1 (GTCS 1)	2
PHT+CBZ+SVP+LEV	2 (GTCS 2)	2(GTCS 2)	4
CBZ+SVP+LEV+CLO	1 (Mixed 1)	0	1
Total	4	4	8

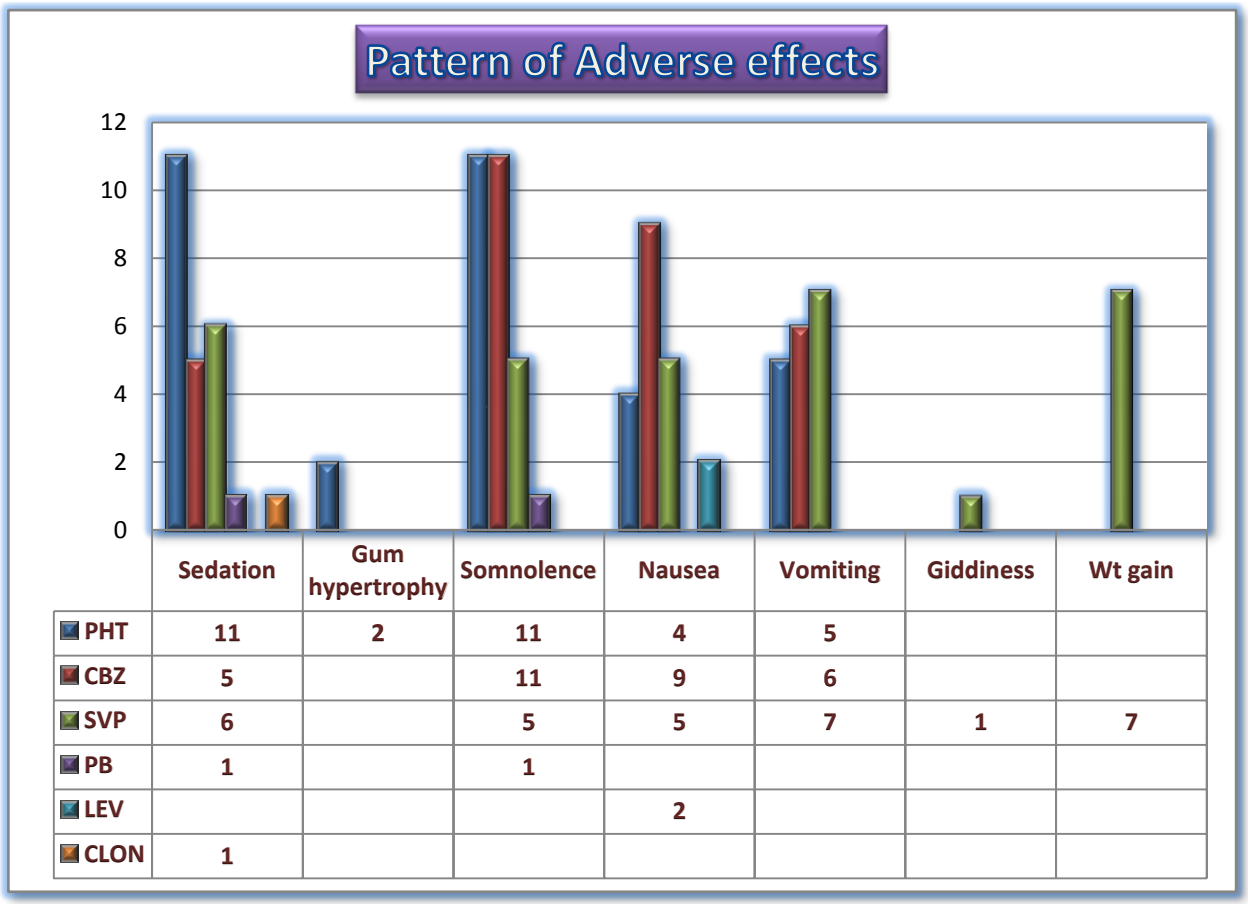
Chi-Square test

	Value	**df**	**Asymp. Sig. (2 sided)**
Pearson Chi-Square	2.000	3	0.572

Four patients were on adequate control with seizure freedom for more than a year. Two patients were on Phenytoin, Carbamazepine, Sodium valproate and

Levetiracetam combination. One each in Phenytoin, Carbamazepine, Sodium valproate, Phenobarbitone combination and Carbamazepine, Sodium valproate, Levetiracetam, Clonazepam combinations respectively.

Pattern of Adverse effects



	Sedation	Gum hypertrophy	Somnolence	Nausea	Vomiting	Giddiness	Wt gain
PHT	11	2	11	4	5		
CBZ	5		11	9	6		
SVP	6		5	5	7	1	7
PB	1		1				
LEV				2			
CLON	1						

The most common adverse effects were somnolence in 28 (14%) patients, sedation in 24 (12%), nausea 20 (10%), vomiting 18 (9%), weight gain 7 (3.5%), gum hypertrophy 2 (1%) and giddiness 1 (0.5%), in the order of decreasing frequency.

33 out of 180 patients (18%) on Phenytoin had adverse effects. Sedation and somnolence (11 patients each) was the most common side effects in patients on Phenytoin, followed by vomiting (5 patients), nausea (4 patients) and gum hypertrophy (1 patient).

31 out of 157 (20%) patients on Carbamazepine had adverse effects. Somnolence (11 patients) was the most common adverse effect, followed by nausea (9 patients), vomiting (6 patients) and sedation (5 patients).

31 out of 144 patients on Sodium valproate had adverse effects. Weight gain and vomiting (7 patients each) were the most common adverse effects, followed by sedation (6 patients), nausea and somnolence (5 patients each) and giddiness (1 patient).Sedation and somnolence (1 patient each) were the side effects in patients on Phenobarbitone, nausea was present in 2 patients on Levetiracetam and sedation was present in one patient on Clonazepam. No patient had life threatening adverse events.

Table.15

Patient characteristics and Demographic profile

Parameters	**Classification**	**N (%)** **Total patients=200**
Gender	Male	123 (61.5%)
	Female	77 (38.5%)
Age (Years)	Mean ± SD, Range	44.56±12.05, 12-71 years
	Mean ± SD, Range (Male)	43.64±12.41, 12-71 years
	Mean ± SD, Range (Female)	46.01±11.39, 18-70 years
Employment	Employed	163 (81.5%)
	Unemployed	30 (15%)
	Student	7 (3.5%)
Educational status	Primary school	56 (28%)
	High school	58 (29%)
	Higher school	2 (1%)
	College	15 (7.5%)
	Illiterate	69 (34.5%)

Table.16

Clinical characteristics of patients with Epilepsy

Disease characteristics	**Description**	**N (%)** **Total patients=200**
Types of Seizures	**Generalized seizures**	**134 (67%)**
	GTCS	125 (62.5%)
	Absence seizure	6 (3%)
	Myoclonic seizures	3 (1.5%)
	Partial seizures	**52 (26%)**
	Simple partial seizure	15 (7.5%)
	Partial seizure with secondary generalization	21 (10.5%)
	Complex partial seizure	16 (8%)
	Mixed seizures	**14 (7%)**
Duration of Seizures	Mean±SD, Range	8.07±5.48, 2-40 years
	< 5 years	37 (18.5%)
	5-10 years	134 (67%)
	10-20 years	20 (10%)

	>20 years	9 (4.5%)
Seizure freedom	Yes (>1 years)	108 (54%)
	Without structural lesions	103/167 (62%)
	With structural lesion	5/33 (15%)
	No (<1 year)	92 (46%)
Structural lesions	**Present**	**33 (16.5%)**
	Gliosis	11 (5.5%)
	Cerebral atrophy	9 (4.5%)
	Calcified granuloma	4 (2%)
	CNS tumors	3 (1.5%)
	MTLS	2 (1%)
	Absent	**167 (83.5%)**
Electroencephalogram (EEG)	Abnormal	72 (36%)
Comorbid illness	DM	16 (8%)
	HT	15 (7.5%)
	COPD	5 (2.5%)
	BA	4 (2%)
Alcohol consumption	Yes	69 (34.5%)

Table.17

Pharmacotherapy characteristics

Pharmacotherapy characteristics	**Description**	**N (%) Total patients=200**
Frequency of AED usage	PHT	180 (90%)
	CBZ	157 (78.5%)
	SVP	144 (77%)
	PB	7 (3.5%)
	LEV	5 (2.5%)
	CLO	2(1%)
Doasage , Mean and Range	PHT	282 mg/d, 100-400 mg/d
	CBZ	1052 mg/d, 200-1400 mg/d
	SVP	1017 mg/d, 400-1400 mg/d
	PB	80 mg/d, 60-120 mg/d
	LEV	1400 mg/d, 1000-1500 mg/d
	CLO	0.5 mg/d
2 drug AED Combinations (113 Patients)	PHT+CBZ	55 (49%)
	PHT+SVP	39 (34%)
	CBZ+SVP	19 (17%)
	Seizure freedom	70 (62%)
	PHT+CBZ	34
	PHT+SVP	25

	CBZ+SVP	11
3 drug AED Combinations (79 Patients)	PHT+CBZ+SVP	74 (94%)
	PHT+SVP+PB	4 (5%)
	PHT+CBZ+PB	1 (1%)
	Seizure freedom	34 (43%)
	PHT+CBZ+SVP	30
	PHT+SVP+PB	3
	PHT+CBZ+PB	1
4 drug AED Combinations (8 Patients)	PHT+CBZ+SVP+LEV	4 (50%)
	PHT+CBZ+SVP+PB	2 (25%)
	PHT+CBZ+SVP+CLO	1 (12.5%)
	CBZ+SVP+LEV+CLO	1 (12.5%)
	Seizure freedom	4 (50%)
	PHT+CBZ+SVP+LEV	2
	PHT+CBZ+SVP+PB	1
	PHT+CBZ+SVP+CLO	0
	CBZ+SVP+LEV+CLO	1

Discussion

Epilepsy is one of the most common neurological illnesses with the same burden as lung cancer in men and breast cancer in women.[27] Studies in recent years have provided more insight into the seizure pathophysiology and management. The ultimate goal of treating epilepsy is adequate control of seizures without side effects. The objective of our study is to analyze the combination Antiepileptic drugs used for managing epilepsy in a tertiary care hospital in South India.

Majority of the patients in our study were in their middle age. The mean age was 44.56 years. Males were slightly younger than females, with mean age of males was 43.64 years and that of females was 46.01 years. The age distribution across other Indian studies were variable, however most patients were between 20-40 years of age.[28,29]Sridharan and Murthy undertook a meta-analysis of the prevalence data obtained from 20 community-based studies on epilepsy in India. According to their analysis, age-specific prevalence rates were higher in second decade for males and third and fourth decades for females.[30] Our patients were slightly older compared to other Indian studies.

Like other Indian studies,[29,30,31] the majority of the patients were males (123 patients). Though employment opportunities are affected in patients with epilepsy

due to social stigma and danger of accidents in workplace, particularly in dangerous jobs like driving, working with machinery, our patients had good employment rate of 81.5%. One third of the patients attending the epilepsy clinic were illiterate (34.5%). Diabetes mellitus and hypertension were the commonly associated comorbid conditions.

The incidence of generalized seizures varies between 45% and 86% in various Indian studies. In our study Idiopathic generalized seizures were the most common seizure type (61%) than partial seizures, a result consistent with many other Indian studies.[29,30,31]Structural lesions were present in 16.5% of patients and it was higher among the patients with partial seizures. Gliosis was the most common structural lesion found in the neuroimaging. Majority of patients had seizure duration between 5 and 10 years with mean duration around 8 years. 54% of patients were free from seizure at the time of analysis, which is comparable to other Indian studies. In a study conducted at Sri ChitraTirunal Institute Medical Sciences, seizure control rate was similar.[28] Seizure control was poor in patients with structural lesions. Only 15% of patients with structural lesions had seizure control, whereas 62% of patients without structural lesions had seizure freedom. This is consistent with other studies which also show poor seizure control in patients with structural lesions.[20,32]

GTCS was the most common type of seizure, seen in 125 patients (62.5%). 71 patients (57%) with GTCS had good seizure control with the combinbation AEDs. Phenytoin was used as the first line drug in 111 patients (55.5%), in which 62 patients (56%) had good seizure control. Carbamazepine and Sodium valproate was used in 6 and 8 patients respectively. Phenytoin and Carbamazepine combination was the most commonly used combination in 41 patients, followed by Phenytoin, Carbamazepine and Sodium valproate used in 38 patients and Phenytoin, Sodium valproate in 33 patients.

Partial seizure with secondary generalization was the next common type of seizure, which was present in 21 patients (10.5%). Carbamazepine was used as the first line drug in 19 patients (90%). Only 5 patients (24%) had seizure control, probably reflecting underlying structural lesions in many of them (17 patients). Phenytoin, Carbamazepine and Sodium valproate combination is used in 14 patients, with only two of them under seizure control.

Complex partial seizure was next in frequency, which was present in 16 patients (8%). Carbamazepine was used in 15 patients with one patient on Phenytoin. 9 out of 15 patients on CBZ and the only patient on PHT had good seizure control.Sodium valproate and Carbamazepine was used in 8 patients. Four patients were on Carbamazepine and Phenytoin combination.

Simple partial seizure was seen in 15 patients (7.5%). All of them were on Carbamazepine. 7 (47%) of them had good seizure control. 6 each were on Carbamazepine with phenytoin and Carbamazepin, Phenytoin and Sodium valproate combination.

Mixed seizure type was seen in 14 patients (7%), which included GTCS associated with either absence seizure or myoclonus. Sodium valproate was the commonly used AED. It was used in 9 patients. 4 patients were on Phenytoin and one on Carbamazepine. Seizure control was obtained in 4 out of 9 patients (45%) treated with SVP. Sodium valproate, phenytoin and carbamazepine was used in 7 patients.

Absence seizure was present in 6 patients (3%). 5 patients were on Sodium valproate, the remaining patient was on Carbamazepine. 3 patients (50%) had seizure control. Sodium valproate, Phenytoin and Carbamazepine combination was used in 3 patients.

Myoclonus was seen in 3 patients. Two patients were on Sodium valproate and one on Phenytoin. All the three were under good control.

Overall the drugs were prescribed according to underlying seizure types most of the times. Carbamazepine was used as the common first line drug in partial seizures, Sodium valproate in absence and myoclonic seizures and Phenytoin was preferred in generalized tonic clonic seizures. However one patient with absence

seizure was on Carbamazepine, one patient with myoclonus was on Phenytoin, one patient CPS was on Phenytoin and five patients with mixed seizures were on Phenytoin or Carbamazepine. These are not the first line drugs for the above conditions, infact some of them are contraindicated.

Phenytoin, Carbamazepine, Sodium valproate and Phenobarbitone are the commonly available antiepileptic drugs in our hospital. Treatment is provided free of cost for patients and the newer antiepileptics are not widely available in our hospital. Hence, majority of Antiepileptic drug combinations contain first generation antiepileptics only.

According to the current knowledge regarding the rational combination of antiepileptic drugs, it has been postulated that antiepileptic drugs with different mechanisms of action are superior to drugs with similar mechanism of action.[18] Because AEDs with similar mechanism of action will have similar side effect profiles, it will result in additive side effects leading to poor compliance or drug withdrawal. The most successful observed AED combination is single mechanism drug combined with a drug that possesses multiple mechanisms of action. This observation is exemplified by the consistent synergistic performance of the combination of Lamotrigene and Sodium valproate in epileptics.[10]

Conventional AEDs (PHT,CBZ, PB,VPA) recorded the highest frequency of use across many Indian studies. Phenytoin was the commonest drug used in 60% of patients and Sodium valproate in 21% of patients in a study conducted at a teaching hospital in Hyderabad .[33]In another Indian study done at Delhi by AhsanHaroon and ManjariTripathi, et al[31] Sodium valproate (38%) was the most common conventional drug used as first line, followed by Carbamazepine (31%) and Phenytoin (20%). Phenytoin was the most common drug used in our study. It was followed by the usage of Carbamazepine and Sodium valproate, Phenobartbitone, Levetiracetam and Clonazepam in various combinations. Phenytoin and Carbamazepine have similar mechanisms of action, blockade of sodium channels. Sodium valproate has multiple mechanisms of action. Phenobarbitone and Clonazepam acts through facilitation of GABAergic inhibition. Levetiracetam acts through modulation of synaptic vesicle protein SV2.

As per the current knowledge, combining Phenytoin or Carbamazepine with Sodium valproate will be beneficial, rather than combining Phenytoin and Carbamazepine. In a study conducted by Brodie and Stephen[34] in Scotland, 2881 patients were studied and 332 patients were on combination AEDs. Lamotrigene/Sodium valproate was the commonest successful duotherapy regimen which was used in 55 patients. Phenytoin/Phenobarbitol was the second

most common used in 29 patients and Phenytoin/Carbamazepine combination was found in 13 patients.

In our study Phenytoin with Carbamazepine was the most common double drug combination. It was used by 49% of patients who were on double AED therapy. 62% of patients on the combination had good seizure control. 31% of patients in the combination had some form of minor adverse effects, the most common being sedation. Though both the drugs have same mechanism of action which is considered to be an irrational combination, our patients had seizure control and adverse events profile similar to double drug combinations containing drugs with different mechanisms of action.[34]

Phenytoin with Sodium valproate was the second most common double drug combination. It was used by 35% of patients on double AED therapy. 64% of patients on the combination had good seizure control. 31% of patients on the combination had some form of adverse effects, the most common being sedation and vomiting.

Carbamazepine with Sodium valproate was the third most common double drug combination, taken by 17% of patients on double AEDs. 58% of patients had good seizure control. 32% of patients had some adverse effects, the most common being nausea.

Phenytoin/Lamotrigene/Topiramate was the commonest effective three drug combination in the by Brodie and Stephen.[34] in our study Phenytoin, Carbamazepine and Sodium valproate was the commonest triple drug therapy, taken by 94% of patients. 41% had good seizure control. 40% of patients had some adverse effects.

Phenytoin, Sodium valproate and Phenobarbitonewas the second most common triple drug combination, taken only by 5% of patients on triple therapy. 75% had good seizure control. 50% of (2 patients) patients had some form of adverse effects.

Phenytoin, Carbamazepine and Phenobarbitone was the least commonly used triple drug combinations, taken by 1% of patients. The patient had good seizure control and had minor adverse effect like somlonence.

In four drug AED combinations, Phenytoin, Carbamazepine, Sodium valproate and Levetiracetam was used in 4 (50%) patients, and seizure control was obtained in 2 (50%) patients. 3 patients (75%) had minor side effects.

Only two patients were on Phenytoin, Carbamazepine, Sodium valproate and Phenobarbitone combination, with seizure control in one patient and minor adverse effects in both the patients.

In other 2 four drug combinations containing Phenytoin, Carbamazepine, Sodium valproate, Clonazepam and Carbamazepine, Sodium valproate, Levetiracetam, Clonazepam, seizures were controlled in the latter combination, with both having minor adverse effects.

There was no five or more drug combintions in our study.

Overall, 54% of patients treated with combination Antiepileptic drugs were free from seizure for more than a year, defined as seizure freedom.[4] The majority of patients under seizure freedom just took two AED combinations.[31,34]All the 3 double drug combinations had similar efficacy in seizure control, around 60% of patients taking the particular combinations. In triple drug combinations, only Phenytoin, Carbamazepine and Sodium valproate combination was taken by majority of patients (94%). Seizure control was relatively poor compared to double drug therapies. Only 41% had good seizure control compared to double drug combinations. Other three drug and four drug combinations were taken only by few patients. Hence their seizure control and adverse effect profiles could not give much information for analysis.

Conclusion

This cross-sectional study examined demographic profile, disease characteristics and prescribing pattern of antiepileptic drugs in 200 epileptic patients on combination antiepileptic drugs in a tertiary care hospital in Chennai, Tamilnadu.

1. Majority was middle aged educated (65.5%) and employed (81.5%) males (61.5%).
2. Idiopathic generalized seizures were more common (61%) than partial seizures.
3. Structural lesions were present in 16.5% of patients and they had poor seizure control.
4. More than half of the patients were treated with two drug AED combinations. 56.5% of patients were maintained on double drug combinations, 39.5% on three drug and 4% on four drug combinations. No combination had more than four drugs.
5. Phenytoin was the commonly used antiepileptic drug in various combinations, Phenytoin and Carbamazepine were the commonly used double AED combination regimen, Phenytoin, Carbamazepine and Sodium valproate were the commonly used three drug AED combination regimen.

6. Antiepileptic drugs of choice for generalized seizures and partial seizures were used in accordance with the recommended guidelines.
7. Though majority of the patients were maintained on older antiepileptics, their efficacy in controlling seizures were comparable to newer antiepileptics. In cost constrained situations older AEDs are as effective as newer and more costlier AEDs.
8. Though AEDs with similar mechanisms of action are generally not preferred due to the concern of additive side effects, they were as effective as other combinations with different mechanisms of action. The adverse events were also comparable.
9. Overall, 54% of patients had good seizure control with the combination AEDs. Seizure control was better with two drug combinations than that of three and four drug combinations
10. 50% of patients reported at least one minor adverse event, which did not require change of drugs. Adverse events were more common with three and four drug combinations than two drug combinations.

Polytherapy remains the mainstay of treatment for large proportion of epileptic patients, particulalrly in cases of refractory epilepsy. Rational ploytherapy is a difficult to achieve and elusive goal with the knowledge available at present. It

needs further research to find the ideal AED combinations. Treatment decision has to be made on an individual basis to make the polytherapy a successful one.

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Annexures

List of abbreviations

AED	Antiepileptic drug
CBZ	Carbamazepine
CPS	Complex partial seizure
CZP	Clonazepam
EEG	Electroencephalogram
ESX	Ethosuximide
FBM	Felbamate
GBP	Gabapentin
GTCS	Generalized tonic clonic seizure
ILAE	International league against epilepsy
LEV	Levetiracetam
LTG	Lamotrigene
NICE	National Institute of Health and Care Excellence
OXC	Oxcarbazepine
PB	Phenobarbitone
PHT	Phenytoin
SVP/VPA	Sodium valproate/ Valproaic acid
TGB	Tiagabine
TPM	Topiramate
VIG	Vigabatrin

PROFORMA

Analysis of Antiepileptic Drug Combinations in Patients with Epilepsy

Name :Date:

Age/Sex: OP/IP No:

Weight: MIN No:

Occupation:

Income:

Address:

Phone number:

Educational status:

Seizure type(s)

S.No	Seizure type	Duration
1	GTCS	
2	Simple partial seizure	
3	Complex partial seizure	
4	Partial seizure with secondary generalization	
5	Mixed	

Time since last seizure:

Antiepileptic drugs used:

Polytherapy:

	AED1	AED2	AED3	AED4
Date of initiation				
Duration				
Starting dose				
Maintenance dose				
Seizure freedom				
Adverse effects				
Compliance				
Reason for poor compliance				
Reason for changing/adding the AED				

Drug history (other than AED):

Menstrual history:

Personal History:

Smoking:

Alcohol:

Sleep pattern:

Other:

Comorbid illness:

SHT:

DM:

CAD:

PT:

HIV/Syphilis:

Others:

Family history:

Marital status:

No of children:

General examination:

CNS examination:

Investigations:

EEG:

CT Brain:

MRI Brain/hippo:

CSF Analysis:

INFORMATION SHEET

- We are conducting a study **"Analysis of the antiepileptic drug combinations in patients with epilepsy"** at the Institute of Neurology, Rajiv Gandhi Govt. General Hospital, Chennai. The purpose of this study is to analyse the use of antiepileptic drug combinations in patients with epilepsy and its rationality with regard to seizure type, seizure control, drug interactions and adverse effects.

- The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

- Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time. Your decision will not result in any loss of benefits to which you are otherwise entitled.

- The results of the study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of the investigator **Signature of the participant**

Date:

PATIENT CONSENT FORM

Study Details : "Analysis of Antiepileptic drug combinations in patients with epilepsy"

Study Centre : Institute of Neurology,
Madras Medical College and
Rajiv Gandhi Government General Hospital,
Chennai - 600 003.

Patient may check (□) these boxes:

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ☐

I understand that the investigator of the clinical study, others working on his behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ☐

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological, EMG, EEG, NCS, Lumbar puncture and muscle biopsy, appropriate to the clinical diagnosis. ☐

I hereby consent to participate in this study. ☐

Signature / Thumb impression: Place : Date :

Patient Name and Address:

Signature of Investigator: Place : Date :

Study Investigator's Name :

Master Chart

S. No	Age	Sex	Seizure type	Duration (Years)	Seizure freedom	Physical Examination	EEG	Structural lesions	AED 1	Dose (mg)	Adverse effects	AED 2	Dose (mg)2	Adverse effects2	AED 3	Dose (mg)3	Adverse effects3	AED 4	Dose (mg)4	Adverse effects4
23	30	M	3	9	1	A	N	0	P	300	1	S	1200	0						
2	18	M	2	4	1	N	N	0	S	1200	0	C	1400	0	P	300	0			
3	18	M	2	6	1	N	N	0	S	1400	0	P	300	1						
4	18	M	1	6	1	N	N	0	P	300	0	C	1200	1	S	1200	1			
5	18	F	1	6	1	N	N	0	P	300	0	S	1200	0	C	1400	1			
10	22	M	1	4	1	N	N	0	P	300	0	S	1400	0						
13	28	M	5	3	1	N	N	0	C	600	0	S	400	0	P	300	0			
16	28	M	3	10	1	N	N	0	S	1200	0	C	1200	0	P	300	0			
19	29	M	1	9	1	N	N	0	P	300	0	C	1400	0						
25	31	F	1	12	1	N	N	0	P	300	0	S	400	0						
26	31	M	6	8	1	N	N	0	C	1200	1	S	600	0	P	300	0			
27	32	M	5	8	1	N	N	0	P	400	1	C	1200	0						
29	32	F	1	8	1	N	N	0	P	300	0	S	1200	1						
34	34	M	1	8	1	N	N	0	P	300	0	C	1200	0	S	1200	0			
36	34	M	1	5	1	N	N	0	P	300	0	S	1200	0						
38	34	M	4	6	1	N	N	0	C	600	0	S	400	0						
41	35	F	1	9	1	N	N	0	P	300	0	S	1200	0						
42	35	F	1	7	1	N	N	0	S	1400	0	P	300	0						
50	37	M	1	7	1	N	N	0	P	300	0	C	1400	0						
54	37	F	6	4	1	N	N	0	C	800	0	S	1200	0						
55	38	F	5	7	1	N	N	0	C	800	0	S	1200	0	P	300	0			
58	38	F	1	3	1	N	N	0	C	1200	0	S	1200	0	P	300	1			
61	38	M	1	9	1	N	N	0	S	1200	0	C	1200	0						
65	39	F	5	14	1	N	N	0	C	600	0	P	200	0						
66	39	M	5	7	1	N	N	0	C	600	0	P	200	1						
72	39	F	7	6	1	N	N	0	S	1200	0	C	600	0						
78	40	M	1	8	1	N	N	0	P	300	0	S	1200	0						
79	40	M	7	12	1	N	N	0	S	1200	0	P	300	0						
80	41	M	1	6	1	N	N	0	P	300	0	S	1200	0	C	1200	0			
81	41	M	1	9	1	N	N	0	P	300	0	S	400	0						
82	41	F	1	10	1	N	N	0	P	300	0	C	600	0						
83	41	F	1	11	1	N	N	0	P	300	0	C	1400	0						
84	41	M	1	9	1	N	N	0	P	400	0	C	1400	1						
88	42	M	1	12	1	N	N	0	S	1400	1	P	300	0	PB	60	0			
90	42	M	1	8	1	N	N	0	P	300	0	S	600	0						
93	42	F	1	8	1	N	N	0	P	300	0	C	1400	0						
97	43	M	1	6	1	N	N	0	P	300	0	C	1400	0	S	1200	1			
100	44	M	5	4	1	N	N	0	C	600	0	S	400	0						
101	44	M	1	8	1	N	N	0	P	300	1	S	400	0						
102	44	F	1	5	1	N	N	0	P	300	0	S	1400	0						
105	45	M	1	2	1	N	N	0	P	300	0	S	1200	0	PB	60	0			
112	46	F	1	7	1	N	N	0	P	300	0	C	1200	0						

115	46	M	4	6	1	N	N	0	C	600	0	P	300	0						
117	47	F	1	8	1	N	N	0	P	300	0	C	1400	0						
127	49	F	4	6	1	N	N	0	C	1200	0	S	1400	1						
128	50	M	5	24	1	N	N	0	C	600	0	S	400	0	P	300	0			
131	50	M	1	6	1	N	N	0	P	300	0	C	1200	0						
134	51	F	1	5	1	N	N	0	P	300	0	C	1400	0						
135	51	F	1	6	1	N	N	0	P	300	0	C	1400	0						
137	52	F	1	5	1	N	N	0	P	300	0	C	1200	0	S	1200	0			
139	52	M	1	9	1	N	N	0	P	300	0	S	1200	1						
143	52	F	6	7	1	N	N	0	C	600	0	P	300	1						
145	53	M	1	8	1	N	N	1	P	300	0	C	1200	0	S	1200	0			
148	53	F	1	8	1	N	N	0	P	300	0	S	1400	0						
150	53	F	1	9	1	N	N	0	P	300	0	C	1400	0						
154	54	F	1	4	1	N	N	0	P	300	0	S	1200	0	C	1200	1			
159	56	M	1	10	1	N	N	0	P	300	0	C	1200	0						
160	56	F	1	3	1	N	N	0	P	300	0	C	1400	1						
161	56	F	7	5	1	N	N	0	P	300	0	S	1200	0	C	600	0			
162	56	F	6	9	1	N	N	0	C	800	0	P	300	1						
164	57	F	1	5	1	N	N	0	P	300	1	S	1200	0						
165	57	M	1	9	1	N	N	0	P	300	0	C	1200	0						
170	58	M	1	4	1	N	N	0	P	300	0	C	1200	0						
172	59	M	1	6	1	N	N	0	P	300	0	S	1200	0						
174	59	F	1	4	1	N	N	0	P	300	0	C	1200	0						
179	61	F	1	7	1	N	N	0	P	300	0	C	1200	0						
183	62	F	1	40	1	N	N	0	C	800	1	P	400	0	S	600	0	L	1500	0
184	62	M	1	7	1	N	N	0	P	300	1	C	1200	0	S	1200	0			
189	63	M	1	12	1	N	N	1	P	300	0	C	1200	0	S	600	1			
190	63	M	1	8	1	N	N	0	P	300	0	S	1200	0						
192	64	M	1	3	1	N	N	0	P	300	0	C	1400	0						
196	66	F	7	7	1	N	N	0	P	200	0	S	1400	0	C	1200	0			
197	67	M	5	8	1	N	N	0	C	800	0	S	1200	0						
21	30	F	1	30	1	A	A	1	S	1200	1	C	1200	1	P	300	1	L	1500	0
37	34	M	3	11	1	A	A	0	S	1400	0	P	300	0	C	1200	0			
9	22	M	2	6	1	N	A	0	S	1200	0	P	200	1	C	1000	1			
12	24	M	7	23	1	N	A	0	S	1200	0	C	1200	0	L	2500	1	CL	0.5	1
15	28	F	7	15	1	N	A	0	P	300	0	S	1400	0						
39	34	M	4	8	1	N	A	0	C	1200	1	S	400	0						
43	35	M	1	6	1	N	A	0	P	300	0	C	1200	0						
45	36	M	1	7	1	N	A	0	P	300	0	S	1400	1						
47	37	F	1	13	1	N	A	0	C	1200	1	P	300	0	PB	90	1			
52	37	F	6	5	1	N	A	1	C	300	1	P	200	0	S	600	0			
62	38	M	1	6	1	N	A	0	P	300	0	C	1200	0						
63	38	M	1	2	1	N	A	0	P	300	0	C	1200	0						
64	38	M	1	13	1	N	A	0	P	100	1	C	1400	0						
68	39	M	1	7	1	N	A	0	S	1200	0	C	1200	0	P	300	0			

77	40	F	1	10	1	N	A	0	P	300	0	S	1200	1								
89	42	F	1	8	1	N	A	0	P	300	0	S	1200	0	C	1200	0					
91	42	M	1	13	1	N	A	0	P	300	0	C	300	0								
96	43	F	1	7	1	N	A	0	P	300	0	C	1200	0	S	1200	0					
98	43	M	1	8	1	N	A	0	P	300	0	S	400	0	C	1200	0					
106	45	M	1	9	1	N	A	0	P	300	1	S	1200	0	C	600	0					
113	46	M	7	8	1	N	A	0	S	1400	0	C	1400	1								
114	46	F	4	5	1	N	A	0	C	600	1	P	300	0								
116	47	F	1	6	1	N	A	0	P	300	0	S	400	0	C	1200	0					
120	48	M	1	35	1	N	A	0	C	300	0	P	200	0	S	1200	1	PB	120	0		
129	50	M	5	12	1	N	A	0	C	600	0	S	600	0								
149	53	M	1	9	1	N	A	0	P	400	1	C	1200	0								
151	53	M	7	14	1	N	A	0	C	1200	0	S	1400	1								
153	54	F	1	2	1	N	A	1	P	300	0	S	1200	1	PB	60	0					
158	55	F	1	9	1	N	A	0	P	300	0	S	1200	0								
163	57	M	1	3	1	N	A	0	P	100	0	S	600	0								
171	59	M	5	3	1	N	A	0	C	600	0	S	1200	0	P	300	0					
182	61	M	4	7	1	N	A	0	C	1200	0	P	300	1								
186	62	M	1	4	1	N	A	0	P	300	0	C	1200	0								
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194	65	F	7	8	1	N	A	0	P	300	0	S	1200	0								
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7	19	F	7	4	0	N	N	0	S	1200	0	P	200	0	C	1200	0					
11	22	M	1	9	0	N	N	0	P	300	0	C	1200	0								
17	29	M	1	8	0	N	N	0	P	300	0	C	600	0	S	1200	0					
18	29	F	1	5	0	N	N	0	P	300	0	S	400	0								
20	29	M	4	3	0	N	N	0	C	800	0	S	1400	1	P	300	1					
22	30	F	1	22	0	N	N	0	P	300	1	C	1200	1								
24	30	M	6	7	0	N	N	1	C	1200	0	P	300	0	S	600	0					
35	34	F	1	2	0	N	N	0	S	1200	0	P	300	0	C	600	0	L	1500	1		
40	35	M	1	3	0	N	N	0	P	400	1	C	1200	0	S	1200	0					
46	36	M	1	3	0	N	N	0	P	300	0	C	1200	0								
49	37	M	1	5	0	N	N	0	P	300	0	S	1200	0								
59	38	F	1	5	0	N	N	0	P	300	0	S	400	0								
60	38	M	1	3	0	N	N	0	P	300	0	S	1200	1								
69	39	F	1	8	0	N	N	0	P	300	0	S	1400	1	C	1200	1					
70	39	F	1	2	0	N	N	0	P	300	0	S	1400	1								
71	39	M	7	10	0	N	N	0	S	1200	1	C	1400	0	P	300	0					
75	40	F	1	11	0	N	N	0	P	300	0	C	1200	0	S	600	0					
76	40	F	1	35	0	N	N	0	S	1200	0	C	1200	1	P	300	1	L	1500	0		
86	41	M	4	5	0	N	N	0	C	600	0	P	300	1								
87	42	M	5	6	0	N	N	0	C	1200	0	S	600	0								
92	42	M	1	8	0	N	N	0	P	300	0	C	1200	0								
94	43	F	1	13	0	N	N	0	P	300	1	C	1200	0	S	600	1					
95	43	M	1	5	0	N	N	1	P	300	0	C	1200	0	S	1200	0					

99	43	M	1	6	0	N	N	0	P	300	0	S	1200	0	C	1200	1			
104	45	F	5	5	0	N	N	0	C	600	0	S	600	0						
107	45	M	1	9	0	N	N	0	P	300	1	C	1200	0						
109	45	M	4	9	0	N	N	0	C	600	1	P	300	0						
110	46	M	1	7	0	N	N	1	P	300	0	S	600	0	C	600	0			
111	46	M	1	7	0	N	N	0	P	400	0	S	1200	0	C	1200	0			
118	47	M	7	9	0	N	N	0	S	1200	0	C	1400	0	P	300	1			
121	48	M	1	11	0	N	N	0	P	300	0	S	1200	0						
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123	49	F	1	2	0	N	N	0	P	400	0	S	1200	0	PB	90	0			
124	49	M	1	8	0	N	N	0	P	300	0	S	1200	0	C	1200	0			
133	51	M	1	6	0	N	N	0	P	300	0	S	1400	1						
138	52	M	1	2	0	N	N	0	P	300	1	C	1400	0	S	1200	1	CL	0.5	0
140	52	F	1	4	0	N	N	0	P	300	0	S	1200	0						
141	52	M	1	3	0	N	N	0	P	300	0	S	1200	0						
152	54	M	5	9	0	N	N	0	C	600	1	P	300	0						
155	54	M	1	11	0	N	N	0	P	300	0	C	1200	0						
157	55	M	5	5	0	N	N	0	C	1200	1	S	400	0						
168	58	M	1	7	0	N	N	0	P	300	0	S	1200	0	C	1400	1			
169	58	F	1	10	0	N	N	0	P	300	1	S	1400	0						
175	59	F	4	4	0	N	N	0	C	1200	0	P	300	0	S	600	0			
176	60	F	1	7	0	N	N	1	P	300	0	S	400	0	C	1200	0			
181	61	F	4	9	0	N	N	0	C	800	0	P	300	1						
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187	62	M	1	9	0	N	N	0	P	300	0	C	1200	0						
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195	65	M	6	4	0	N	N	1	C	600	0	P	300	0	S	1200	0			
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74	39	M	4	9	0	A	N	1	C	800	0	P	100	0	S	600	1			
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33	33	M	6	6	0	A	A	1	C	600	0	P	100	0	S	600	0			
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108	45	M	6	2	0	A	A	1	P	300	0	S	600	0	C	1200	1			
178	60	F	6	9	0	A	A	1	C	800	1	S	400	0	P	300	0			
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48	37	M	1	11	0	N	A	0	P	300	1	S	1200	0						

53	37	F	6	8	0	N	A	1	C	600	0	P	300	0	S	600	1				
56	38	F	5	9	0	N	A	0	C	600	0	S	1200	0							
57	38	M	1	9	0	N	A	0	P	300	0	C	1200	0	S	1200	1				
67	39	M	1	12	0	N	A	0	P	300	1	C	1200	0	S	600	0				
103	44	M	6	10	0	N	A	1	C	800	0	S	400	0	P	300	0				
119	47	F	4	5	0	N	A	1	C	200	0	P	300	0	S	600	0				
125	49	M	1	7	0	N	A	0	P	100	0	C	1400	0							
126	49	F	6	9	0	N	A	1	C	800	0	P	300	1	S	600	1				
130	50	M	1	3	0	N	A	1	P	100	0	C	1200	0							
136	52	M	1	9	0	N	A	0	P	300	0	C	1200	0	S	1200	0				
142	52	M	1	8	0	N	A	0	P	100	0	C	1200	0							
144	53	M	1	9	0	N	A	1	P	300	0	C	1200	1	S	1200	1				
146	53	M	1	6	0	N	A	1	P	300	0	S	1200	0	C	600	0				
147	53	F	1	9	0	N	A	0	P	300	0	S	1400	0	C	1400	1				
156	54	M	6	10	0	N	A	1	C	600	0	S	600	0							
166	57	F	4	3	0	N	A	1	C	600	1	P	300	0	S	1200	1				
167	58	M	5	10	0	N	A	0	C	600	0	S	1200	0							
173	59	M	1	27	0	N	A	0	C	300	1	P	200	0							
177	60	M	1	11	0	N	A	0	P	100	0	C	1200	0							
14	28	F	1	26	0	A	A	1	S	1200	1	C	200	0	P	300	1	PB	120	1	
31	32	M	6	2	0	A	A	1	S	1200	0	C	600	0							
132	50	F	6	3	0	A	A	1	C	1200	1	P	100	0	S	1200	1				
200	71	M	6	7	0	A	A	1	C	1200	1	P	300	0							

GTCS 1	Seizure fre	NORMAL - N	NO -O	PHT - P
ABSENCE 2	Yes - 1	ABNORMAL - A	YES- 1	CBZ - C
MYOCLONUS 3	No - 0			SVP - S
SPS 4				LEV - L
CPS 5				CLO - CL
PARTIAL WITH SEC GEN 6				PB - PB
MIXED 7				

AE -1
No AE - 0

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No : 044 25305301
Fax : 044 25363970
EC REgNo:ECR/270/Inst.TN/2013

CERTIFICATE OF APPROVAL

To
Dr.S.Balasubramaniam,
PG in Neurology,
Institute of Neurology,
Madras Medical College&RGGGH,Chennai-3.

Dear S.Balasubramaniam,

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "Analysis of Antiepileptic drug combinations in patients with epilepsy" No.02062013.

The following members of Ethics Committee were present in the meeting held on 11.06.2013 conducted at Madras Medical College, Chennai -3.

1. Dr.SivaKumar, MS FICS FAIS --- Chairperson
2. Prof. R. Nandhini MD -- Member Secretary
   Director, Instt. of Pharmacology ,MMC, Ch-3
3. Prof. Shyamraj MD -- Member
   Director i/c , Instt. of Biochemistry , MMC, Ch-3
4. Prof. P. Karkuzhali. MD -- Member
   Prof., Instt. of Pathology, MMC, Ch-3
5. Prof. A. Radhakrishnan MD -- Member
   Prof of Internal Medicine, MMC, Ch-3
6. Prof. S. Deivanayagam MS -- Member
   Prof of Surgery, MMC, Ch-3
7. Thiru. S. Govindsamy. BABL -- Lawyer
8. Tmt. Arnold Saulina MA MSW -- Social Scientist

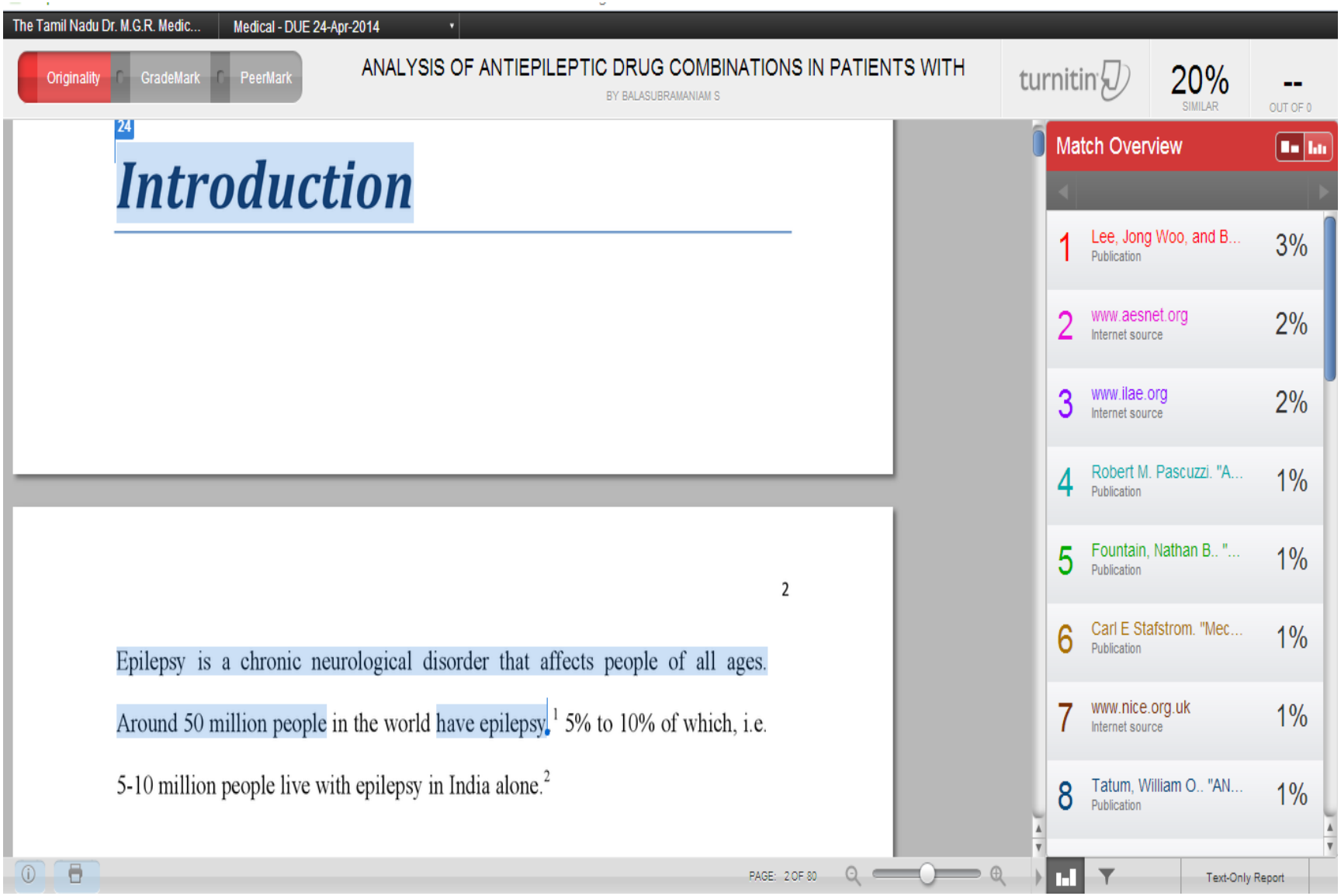
We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

R Nandhini 12/7/13
Member Secretary, Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003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2
Epilepsy is a chronic neurological disorder that affects people of all ages.
Around 50 million people in the world have epilepsy.[1] 5% to 10% of which, i.e.
5-10 million people live with epilepsy in India alone.[2]
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